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SOCIETY OF UNIVERSITY SURGEONS

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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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Original Communications

Society of University Surgeons

Problems in Surgical Training. Eugene M. Bricker, M.D., St. Louis, Mo. ---------- 337

Cardiopulmonary Dynamics of Mitral Stenosis. Ivan D. Baronofsky, M.D., and Francis J. Haddy, M.D., Minneapolis, Minn., Allan L. Ferrin, M.D., Salem, Ore., and Craig W. Borden, M.D., Minneapolis, Minn. ---------- 347

Changes in the Pulmonary Vessels Produced by Experimental Pulmonary Hypertension. William H. Muller, Jr., M.D., J. Francis Dammann, Jr., M.D., and William H. Head, Jr., M.D., Los Angeles, Calif. ---------- 363

Certain Physiologic, Pathologic, and Surgical Features of Complete Transposition of the Great Vessels. C. Walton Lillehei, M.D., and Richard L. Varco, M.D., Minneapolis, Minn. ---------- 376

Controlled Unilateral Bronchovascular Occlusion as a Method for Studying Pulmonary Function. Paul Nemir, Jr., M.D., H. H. Stone, M.D., T. N. Mackrell, M.D., and H. R. Hawthorne, M.D., Philadelphia, Pa. ---------- 401

Progressive Infantile Emphysema. J. L. Ehrenhaft, M.D., and Rodman E. Taber, M.D., Iowa City, Iowa ---------- 412

(Contents continued on inside back cover)

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SURGERY

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SURGERY

VOL. 34 SEPTEMBER, 1953 No. 3

Original Communications

Society of University Surgeons

PROBLEMS IN SURGICAL TRAINING

THE PRIVATE NONUNIVERSITY HOSPITAL

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ST. LOUIS, MO.

IN THE past thirty years there has been enormous progress in the development of the residency system of training surgeons introduced so effectively by Halsted. The fundamental principles of the residency system are widely accepted in this country, and the number of institutions equipped with clinical and laboratory facilities and staffed with personnel adequate for the conduct of this type of training has steadily increased. Training surgeons by this system has been recognized as surpassing all others and its promotion is one of the stated aims of this Society. Considering these facts it is our responsibility to keep the problems facing the training of surgeons clearly before us. The recognition and definition of these problems may be as difficult as their eventual solution.

Of the problems facing surgical training today one of the most difficult is presented by the nonuniversity private hospitals in their efforts to maintain approved residency programs. This problem should interest us as university surgeons, for approximately 50 per cent of the approved training services for general surgery today are in private hospitals without university connection. The fact that such a large segment of surgeons comes from this source lends emphasis to the importance of the quality of training in these hospitals, and to the problems encountered in maintaining training services in them. Furthermore, any expansion of training facilities in the future may have to come largely from these institutions.

Before embarking upon this discussion, recognition should be extended to the important events that have led up to our present position in surgical training, some of which have a direct bearing on the difficulties of private hospitals maintaining approved training services. Of fundamental importance have been the activities of the American College of Surgeons in hospital standardization, culminating in recent years in the sharing of this responsibility with the

Presidential address, presented at the meeting of the Society of University Surgeons, Feb. 13, 1953.

American Medical Association, the American Hospital Association, the American College of Physicians, and the Canadian Medical Association through the Joint Commission on Accreditation of Hospitals. Another milestone was reached with the establishment of the American Board of Surgery in 1937. Whereas the American College of Surgeons had established a set of minimum requirements which allowed a physician to distinguish himself as a surgeon by securing fellowship, the American Board of Surgery established a higher set of requirements which added immeasurable impetus to the gradually growing residency system. In recent years the requirements for fellowship in the American College of Surgeons have approached those of the American Board of Surgery for certification and although originally established for different purposes it is possible that the time will arrive when the requirements of the two organizations will be identical and there will be one examining and certifying body for advanced surgical achievement. A very important unifying step in this direction has been made in the past few years in the establishment of the Conference Committee on Graduate Training in Surgery composed of members of the American Board of Surgery, the American Medical Association, and the American College of Surgeons. This organization provides a single agency for the examination and approval of surgical training services and insures that the evaluation will be done by men experienced in training surgeons.

These important events have set the stage for American Surgery as we find it today. In 1952 there were 490 general surgery residencies approved by the Conference Committee on Graduate Training in Surgery. In the same year, 1,176 surgeons were initiated into the American College of Surgeons and 745 surgeons passed the American Board of Surgery examinations. Our own Society has played a part in this evolution. Organized in 1938 with ten member institutions, there are now thirty-seven training centers throughout the United States and Canada whose aims and high standards of training have brought them together in the Society of University Surgeons. Yearly, more university training services are being added to our ranks. There is no other organization in which the problems of surgical training could be discussed before a more uniformly able or critical audience.

It should be acknowledged early in a discussion of the private hospital problem that some such institutions have long maintained resident training services of excellent quality. These services have usually been built up around individuals with a knowledge of the residency system and with a desire to teach. Over the years in these hospitals the customs and traditions of a training service have become established. Other hospitals in the past have succeeded to a lesser degree in this effort and now many more are endeavoring to establish effective training services under great difficulty. Several questions might be asked. Is there an actual need for the training facilities of private hospitals? What factors contribute to their difficulty in obtaining residents and in securing approval of their programs? Is there a pattern that might be expected to solve these difficulties, and how do the university training centers fit into the picture?

To determine whether or not there is an actual need for the training facilities of private hospitals leads to the question of whether an adequate number of surgeons is now being trained. Satisfactory factual information on this subject is not available. However, there are several observations that can be drawn upon to get an indication of the answer. The rapid increase in the number of surgeons seeking qualification in recent years (from 350 certified by the American Board of Surgery in 1947 to 745 in 1952) can only be a reflection of the need for these specialists. There is no indication yet that the saturation point has been reached, or even closely approached. It is not possible to base an estimate of the requirements for trained surgeons on any past criteria. Many factors are changing so rapidly that it is only possible to look forward and estimate what the needs of the future will be. The rapid population increase (expected to reach 171 million by 1960), the tremendous volume of industrial accidents (2.1 million in 1951), the tragic rise in highway accidents, the increasing life expectancy of the population and the resultant increase in degenerative diseases and cancer requiring surgery, the increasing repertoire of operative procedures made possible through advances in all the ancillary sciences, and the increasing number of procedures that require long operating time—all these factors are adding steadily to the sum total of surgery to be done. At the same time the enlargement of medical centers and the building of many community hospitals are providing beds and facilities that make it possible to carry surgery to more people.

To consider the problem further from available figures we find that there are 20,000 physicians listed in the directory of the American Medical Association as limiting their work wholly or partly to general surgery. A spot check of various known communities demonstrates that there are considerably more who do surgery but have not so indicated in the information supplied to the American Medical Association. But, if 20,000 is assumed to be the correct number representing the total of general surgeons in the country, the number trained each year to take care of loss from the attrition of age and retirement would have to be in the neighborhood of 1,000 (taking 5 per cent to represent the combined attrition). An interesting check on this figure is the number of deaths in the fellowship of the American College of Surgeons per year. In the first ten months of 1952 there were 355 reported deaths from the total fellowship of 18,500, or an estimated loss for the year from death alone of 430 surgeons.

Another important consideration is the amount of surgery currently being done by physicians with little or no formal training in surgery who are largely unrepresented in the American Medical Association directory in the 20,000 who call themselves surgeons. It is a conservative estimate, based partly on an unpublished survey that indicates an even higher figure, that 25 per cent of surgery the country over is not done by specialists in surgery. If this is taken as an indication that more surgeons should be trained in order to take care of this 25 per cent of the surgery it could be shown that the yearly output should be raised to 1,300 to supply the need. These figures would not

take into consideration the expanding population or the expanding field of surgery but would simply indicate the requirements to take care of the volume of surgery as it exists today.

Many of the fallacies in these speculations are too obvious to take time for comment here. However, they lend support to the hypothesis that the demand for trained surgeons is far from being exhausted and that the facilities for training to completion today are inadequate to meet the demand. Why is it that this discrepancy between the available supply and the theoretical demand is not more apparent? One of the important reasons is that there are many surgeons who get two or three years formal training in surgery but are unable to finish and, therefore, go into practice with this background. This group of surgeons will be discussed later. Another reason is that there are a number of physicians who practice surgery with little or no recognizable formal training after medical school and an internship. The numerical importance of this group is impossible to determine but is probably very significant.

It can be pointed out that the increasing number of surgeons certified by the American Board of Surgery yearly, and the increasing number of approved residencies in general surgery, are an indication that the gap between supply and demand is rapidly being eradicated. This is quite true. But, it is also an indication of the relative importance of the private nonuniversity hospitals with approved residencies in general surgery that are in existence now, and of more that will exist in the future. From what other sources can we expect future residency services to develop?

Although there are some excellent programs in Government controlled institutions, it is certainly to be hoped that the output from this source will not be increased further through the building of more Veterans Administration and military hospitals. No such increase is anticipated. Also, it is unlikely, with health insurance on the increase as it is, that it will be found necessary for many cities or communities to add materially to their charity beds in the foreseeable future. However, the development of new medical schools and the expansion of old ones should add materially to the output of trained surgeons in coming years. There are now 80 medical schools in this country, 74 of which are four-year schools. It is quite possible that as many as twenty more four-year schools will be established in the next twenty years including six present schools that will expand from two to four years. The yearly output of finished general surgeons from the clinical facilities of each teaching center, as judged by the number that finish the top residency positions, would be perhaps two or three. If the latter figure is accepted and if half the present schools increase their output of finished surgeons by one per year, we have an estimated increase of approximately 100 surgeons per year. This source of increase can be counted upon but it will be slow in developing and at the end of twenty years will just about balance the expected population increase, the relative supply of completely trained surgeons remaining about the same as today. In view of these predictions regarding the training of surgeons in the future it seems evident that the important position held today by the private hospital will be maintained

and perhaps even increased. Certainly the problems facing the institutions producing such a large proportion of our trained surgeons deserve very careful scrutiny.

Before leaving the subject of supply and demand in surgery and before progressing with a discussion of the problems of private hospitals, it seems justifiable to digress briefly to consider that group of surgeons with some formal training but not enough for qualification by the American Board of Surgery. Many of these physicians practice surgery as a specialty and many do surgery with general practice. Regardless of the rapid strides made in producing fully qualified surgeons, the fact remains that there are not enough being trained to take care of the population needs, and it may be years before this desirable state is reached. Until that time, as in the past, the man who has had an internship plus two or three years training in surgery can fill a very important gap in the needs of the public. The more of them who go into practice the fewer opportunities there will be for men of lesser training. Why cannot the need for men of this background be recognized to the point that it can be made to serve as a goal rather than as a consolation? Two or three years on a properly run and properly staffed residency service are enough to instill an individual with the fundamental principles of surgery, and with a clear recognition of his own limitations. If more physicians with this type of background could be channeled into general practice there would be better surgery for the public at ground level. Such a suggestion need not mean that the maximum standards for qualification would be lowered, but rather that the minimum standard for the practice of surgery should be raised. The way should be left open for surgeons of this class to keep abreast and to reach complete qualification through opportunities for further training if they so desire. Such a suggestion does not embody anything new, for exactly this very thing is being done now. But it is not being done with a very clear recognition of the important role it plays in American surgery. If it were encouraged, the minimum standard of surgery would certainly be raised and some of the causes for the existence of unethical practices would be eradicated. A young surgeon with a background of experience on a properly run and staffed training service will be a poor candidate for financial dickering if he is able to stand on his own feet in the beginning through the development of his own general practice. He should be a better surgeon as a result and the needs of the public would be better served. To look forward into the future it can be imagined that the recognition of this need in American surgery might lead eventually to the establishment of a minimal standard required by law. Thus far we have concentrated single-mindedly on the training of surgeons to what we consider completion and have given little thought to the possibility of other needs, except for an occasional resigned philosophical comment as the common duct strictures continue to arrive for repair.

To return to the problems of private hospitals, what factors are contributing to their difficulties in maintaining approved programs? Two immediate factors are easily recognized. First, as a result of the entrance into the field

of specialty training of the Army, the Veterans Administration, and the United States Public Health Service, and as a result of the requirements of our sustained military force, the supply of applicants for both internships and residencies has been greatly diminished. Second, and of much more long-term importance, the accrediting agencies have become more effective and withhold or withdraw approval from those hospitals not measuring up to a satisfactory standard. Furthermore, in general surgery any confusion regarding approval has been clarified by the establishment of a single accrediting body composed of representatives of the American Board of Surgery, the American College of Surgeons, and the American Medical Association. This is one of the most progressive developments affecting surgical training in recent years and it is to be hoped that it endures. It has resulted in spotlighting the deficiencies of private hospitals, and with clear definition, these deficiencies stand a better chance of being resolved.

It is beyond the scope of this presentation to go into detail regarding the development of training services in private hospitals. However, two problems are of basic importance and will be discussed. They pertain to the fundamental requirements for a good surgical training service which are: (1) adequate clinical material, and (2) an adequate teaching staff. Many private hospitals have difficulty with both.

Clinical Material.—The big problem today in private hospitals is the maintenance of enough ward or service beds to allow completion of training through a system of graduated increasing responsibility. An adequate volume of surgery through such beds is important, although the volume need not be great to be adequate. Ten ward beds properly utilized, in a hospital with an active private surgical service, can be made adequate for a four-year surgical program. These beds need not be for the completely indigent only, but also for those of limited finances who would have difficulty in paying for hospitalization and private medical service without undue hardship. The beds will represent a cost to the hospital and should be administered as economically and efficiently as possible by the medical staff. The establishment, development, and conduct of such a ward service in a private hospital is a fundamental necessity which must be recognized and supported by both administration and medical staff. Its development provides the basic element necessary for the preservation of the Halsted system of training surgeons which has been proved to surpass all others and which should not be allowed to become a casualty of the changing times. It is to be expected that the cost of such a program will be criticized by the administration, and the principle of relinquishing patients to it will be viewed skeptically by the staff. Both of these difficulties are surmountable. Most hospitals of adequate size to desire a residency training program in surgery will always have a fair share of indigent or semi-indigent patients. These patients will be found scattered about the hospital on the services of various staff members, many of them disposal problems and few of them of any teaching value. Organization and the proper use of such beds may add some to the hospital deficit, but can add enormously to the effectiveness of a training service.

The source of clinical material for the training beds will vary for each institution. An outpatient department is a necessity, not only as a source of clinical material but as an important part of the training program through the work-up and follow-up of patients. Arrangements with outside county, city, religious, and fraternal institutions can produce a scattering of acceptable patients. A good hospital will always have a few unattached people with insufficient funds applying for help through the front door or through the outpatient department. One of the most effective sources of patients is the staff itself, who, if cooperative, can refer an appreciable number of suitable and economically eligible patients from their offices to a training service. The failure to maintain effectively a nucleus of ten surgical beds for service patients in a hospital of 250 beds or over is a plain indication of the lack of interest, cooperation, and effort on the part of the staff or administration, or both.

One factor that has added to the difficulty of securing an adequate amount of clinical material for service beds has been the growth of hospitalization and medical service insurance. University training centers have felt the impact of this force as well as the private hospitals. A solution to this problem is not yet in effect but must be found, for it is entirely possible that in the near future that segment of the population unable to afford voluntary insurance, and not insured by industry or by some other means, will have its insurance paid for from State or Federal funds. When this day comes, the day of the purely indigent patient will be past and with it is very likely to go the progress of the past thirty years in development of the residency training system unless something is done to solve the problem now. The essence of this problem lies in determining whether insured patients should be operated upon by members of the resident staff, and the method of collection of the insurance fee. The chief difficulty in finding a solution thus far has resulted from a lack of united opinion as to how it should be solved on the part of the medical profession itself. There is no valid reason for trained residents under the supervision of responsible surgeons to be considered ineligible to care for insured patients on the ground of professional qualifications. The only objection then will arise as a result of the collectable fee. If surgeons are to be trained in the best manner possible it is up to the medical profession to decide so, and a positive decision will mean maintenance of a nucleus of service beds. In order to do this it is mandatory that some adjustment be made for the growth of health insurance that will allow insured patients to be admitted to ward training services if the patients so desire. Patients will so desire in proportion to the reputation of the institution and the quality of care and attention that is given by the resident and attending staff. The establishment of this policy simply awaits approval of the medical profession. Cooperation of the insurance companies will follow. It would be preferable if the policy were established at a national level. Thus, the organized representatives of the medical profession would agree with the insurance companies that patients of certain economic levels would be eligible for admission to the beds of training services approved

by the recognized accrediting agencies, the patient to enter the training service of his own free will and with complete understanding, the fee to be collected by the head of the service to be used for the support and improvement of the training program. If such a national policy is not forthcoming the same thing could be accomplished at a state or local level. But, at any level the support of the practicing members of the medical profession will be necessary.

Another possible solution lies in the elevation of residents to bona fide members of the hospital staff, thus changing their status to that of practicing surgeons. Such a plan has merit and deserves further consideration and trial. However, approval and cooperation of the practicing profession would probably still be necessary since the policies governing the single largest insurance plan are largely determined by the medical profession (Blue Shield plans account for 40 per cent of all medical service insurance).

The question of what to do about the large group of indigent patients that may in the future be insured by State or Federal funds is a very pertinent one. When and if this time arrives the medically indigent will no longer exist. The needs of medical schools and training centers must be taken into account as the policies pertaining to the care of these patients are formulated. It is hardly conceivable that arguments against their admission to training centers could be advanced. It is reassuring to know that the problems presented by the insured indigent patient and the needs of medical education are now being considered by responsible committees of the American Medical Association and the American Association of Medical Colleges. Patients with voluntary health insurance should be considered at the same time and at the same level. It is imperative that the way be left open for medical education to have access to adequate clinical material to accomplish its purpose. We must not be forced back to preceptorships for training in surgery.

Another factor that should be considered in a discussion of the clinical material of private hospitals is the value of private patients in surgical training. There is no doubt that surgeons can be trained on an all private service. A period on a good private service is one of the most valuable experiences that can be given a young surgeon. However, no one acquainted with a well-established ward service with an adequate volume of patients and an active and interested attending staff would ever admit experience gained on it could be equalled by experience gained from a private service alone. The use of private services deserves more consideration than has been given in the past, but there are limitations that cannot be overcome. The extent to which training by this method can be carried will be determined by the conscience of the individual surgeon. It seems the concensus of opinion that any practice that does not insure the knowledge and approval of the patient is not to be desired. It, therefore, appears evident that the clinical material for resident training from this source will be limited, except in certain types of institutions where the differentiation between teacher and trainee is indistinct and where the custom has already been established that the residents take an active part in the care of private patients. Institutions in which this situation prevails are usually staffed

partly or completely by full-time personnel. Although this pattern has some advantages so far as training is concerned it is hardly a pattern that can be followed extensively by private hospitals.

Teaching Staff.—The organization of the staff of a private hospital in order that it may be effective in the teaching and training program requires primarily that authority be delegated to a responsible individual. This individual must be both a teacher and administrator; he must know what surgical training is, and how to do it. These seem perfectly obvious statements, yet to get a staff to reorganize for the purpose of establishing a training service under the direction and responsibility of one of its capable members is like trying to speed up the processes of evolution. The hospital staff that can do this of its own volition is unique, yet, it should be accomplished by the staff. Occasionally, the administration or governing board of the hospital may have insight into the problem and force the staff into action, or take action for them. This sounds highly critical of the hospital staff and its democratic processes. Unfortunately, the criticism is too often justified. The basic requirement for success, delegation of authority to a capable individual who is willing to accept it and the accompanying responsibility, is an act difficult for a hospital staff to consummate. It is much safer and easier to appoint a three-man committee every year or so. Unfortunately, a committee lacks the driving force of ambition and the disgrace of failure is diluted by its number and softened by its anonymity. The same cannot be said of a responsible individual. Need an organized hospital staff be an agency dedicated to the maintenance of the status quo? Or, should it not be an agency capable of recognizing its needs and willing to take vigorous corrective action in the form of advancing and using its capable members? As the competition for resident staffs has become more intensified in the past few years this point has become apparent in several areas, and hospitals with excellently planned and executed programs under capable individuals are beginning to appear. It could be said that the shortage of residents precipitated by the renewed military demands of the Korean war and the concomitant development of the joint Conference Committee on Graduate Training in Surgery have resulted in stimulating a rejuvenation of training programs in private hospitals. This is in marked contrast to the period immediately after World War II when almost anything was accepted as surgical training, and "I want my boards," as so aptly described by one of our members* was the battle cry of the young trainee forced into accepting almost anything in order to get them.

A training service in a private hospital, then, requires an adequate staff of qualified surgeons, capable and organized for effective teaching and supervision of the residents and under the direction of an individual who has the authority, the desire, and the ability to make the program work. This accomplished, a private hospital with adequate clinical material can train surgeons properly and to completion. The university training services can play an important role in the development of private hospital training programs through

*Bowers, Ralph F.: Observations of Surgical Training, SURGERY 23: 377-388, 1948.

supplementing both clinical material and teaching staff. Perhaps the most practical contribution of the established university training service is through the men who come from it to carry the ideas and methods of good surgical training to the nonuniversity hospitals. In some instances it may be possible to work out an exchange or affiliation mutually beneficial, trading a rotation on the facilities of an excellent private service in one hospital for the advantages of a well-run ward service in another. At any rate, the possibilities of the local university medical center should be sought by the nonuniversity hospital, and it should be the aim of the university to assist these hospitals in any way it can to raise their professional standards and standards of training as high as possible.

SUMMARY

It appears that there is a definite need for the training facilities of nonuniversity private hospitals and that this need will increase in the future. In view of the numerical significance of these institutions in the training of surgeons it is of great importance that they maintain training programs of a high standard. It should be insisted that these training programs embody the basic principles of the Halsted system, which provides for a part of the training period to be spent on a service where a major portion of responsibility can be delegated to the resident staff under the supervision of capable attending surgeons. To supply this need in private hospitals requires the careful marshalling of available sources and funds for the maintenance of an adequate nucleus of service beds, and the effective organization of the staff for teaching.

University medical centers should recognize the need for surgical training services in private hospitals and should cooperate by every means possible to make these services of high quality.

It is the responsibility of the medical profession to see that the growth of health insurance is accompanied by the formulation of policies that will make it possible for good training programs to continue. These policies should provide for the admission of patients of selected economic levels with medical service insurance to ward training services, if the patients so desire. If completely indigent patients are to be insured by State or Federal funds in the future, the needs of surgical training and of all medical education must be integrated with this profound social change in order that advances in these fields of recent years will not be nullified.

The use of private clinical material for surgical training should be developed as much as possible, but should not be considered as being adequate to supplant completely the experience to be gained from service beds. Especially is this true in surgical training.

CARDIOPULMONARY DYNAMICS OF MITRAL STENOSIS

A Clinical and Experimental Study

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INTRODUCTION

THE recent acquisition of new techniques in cardiac surgery has led to an increased demand for a better understanding of the physiology of many cardiovascular lesions. Cardiac catheterizations in the human being have given much valuable information; however, it is natural that certain insufficiencies in our knowledge will not be filled because of inherent dangers to individuals in subjecting them to certain diagnostic techniques, such as left heart catheterization. It is, therefore, necessary to resort to the experimental animal in order to fill these gaps. A clear knowledge of the mechanisms of disease inevitably leads to a better understanding of both the therapy and the results of therapy.

It is the purpose of this report to present the cardiopulmonary changes occurring as a result of mitral stenosis. These data were obtained from both the experimental animal and the human being.

METHODS

In the Animal.—Mongrel dogs were anesthetized with intravenous pentobarbital sodium 33 mg. per kilogram approximately two weeks before and two weeks to seventeen months after production of experimental mitral stenosis by the method previously described.[1] With the animal supine, cardiac catheters were introduced into the pulmonary artery and a pulmonary vein.[2] An endotracheal tube was employed, and the animal was connected to a closed-system spirometer containing 100 per cent oxygen. Pulmonary artery, pulmonary vein, intrathoracic, and femoral artery pressures were simultaneously recorded with standard resistance wire pressure transducers (Statham strain gauges). Zeros were arrived at by visualizing the tips of the catheters fluoroscopically and exposing the strain gauges to atmospheric pressure at that level. The catheter in the pulmonary vein was immediately withdrawn into the left ventricle and blood samples were obtained from the two catheters for determination of the cardiac output by the direct Fick method. T-1824 dye, 7.5 mg., was injected into the pulmonary artery and blood samples were collected from the catheter in the left ventricle for determination of the cardiac output

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by the dye method. The catheter in the pulmonary artery was withdrawn into the right atrium and the pressure recorded. These measurements and collections consumed an eight-minute period during which oxygen consumption was measured. In addition, simultaneous recordings were made of pulmonary "capillary" or wedge pressures and pulmonary vein pressures.

Integrated mean pulmonary vascular, right atrial, intrathoracic, and femoral artery pressures were measured with a compensating polar planimeter, and all intrathoracic vascular pressures were expressed in relation to the general intrathoracic pressure as zero. Oxygen content of the blood samples for estimation of the cardiac output by the direct Fick method was determined by the Van Slyke manometric method.[3] Cardiac output by the dye injection technique was calculated according to the method of Hamilton and associates,[4] except that collection of the blood samples from the left ventricle obviated the necessity of extrapolating the curves to zero. Using Rubner's constant in Meeh's formula, $11.2 \sqrt[3]{(\text{Wt. in gm.})}$,[2] to calculate surface area, cardiac output was expressed as cardiac index. Using Stewart's formula (volume = $\frac{\text{mean circulation time} \times \text{cardiac index}}{60}$),[5] the volume of blood contained in the lungs and the left heart, the so-called central blood volume, was determined. In the dogs that died, the mitral orifice was opened and laid flat and the circumference was measured. Since the orifices were circular, the area was calculated from the circumference. The area was then expressed per square meter body surface area. Pulmonary resistance was calculated from the formula $R = \frac{\text{pulmonary pressure gradient}}{\text{cardiac index}}$. The pulmonary pressure gradient was obtained by subtracting the pulmonary vein pressure from the pulmonary artery pressure. Gorlin's formula[6] was used to calculate the effective area of the mitral valve.

In the Human Being.—A total of 63 patients were studied; in particular, preoperative studies for 31 patients were repeated postoperatively in approximately six weeks and, in five instances, one to two years following surgery. Right heart catheterization was performed using techniques previously described.[7, 8] Pulmonary capillary or wedge pressures were measured in 6 patients.[9] Integrated mean pressures were used in the comparative analyses. Using a modification of Stewart's method,[5] the volume of blood contained in the lungs, the left heart, and great vessels, the so-called central blood volume, was determined in 13 patients. The total blood volume was also determined. The total lung volume was measured in 18 patients. The functional residual volume was determined by the open circuit method.[10] The vital capacity and its subdivisions were recorded with a spirometer.

RESULTS

Pulmonary Artery and Vein Pressures.—

In the animal: In the experimental animal chronic mitral obstruction was effectively produced by the method of Ferrin and associates.[1] In a group of 10 animals studied pre- and postoperatively, only 2 failed to show a significant

increase in the pulmonary vein pressure. The average increase was about two and one-half times normal, while the range was from two to five times the preoperative level (Table I.).

TABLE I. PULMONARY VASCULAR PRESSURES IN MILLIMETERS OF MERCURY IN 10 DOGS BEFORE AND AFTER PRODUCTION OF MITRAL STENOSIS

DOG NUMBER	PREOPERATIVE		POSTOPERATIVE		PRESSURE INCREASE (VEIN)
	PULMONARY VEIN	PULMONARY ARTERY	PULMONARY VEIN	PULMONARY ARTERY	
1	6.8	22.4	15.9	21.2	2×
2	12.4	19.1	13.7	20.2	—
3	11.0	21.0	9.6	15.3	—
4	10.8	25.3	25.9	35.4	2½×
5	9.8	17.8	25.4	26.0	2½×
6	7.9	19.9	17.9	25.4	2×
7	6.0	18.0	25.9	28.4	4×
8	8.7	17.6	17.2	24.0	2×
9	4.9	17.6	26.2	35.8	5×
10	9.0	18.6	17.7	25.2	2×

Table II presents the summarized data from 85 separate catheterizations in 73 dogs before and after the production of mitral stenosis. It shows the frequency of distribution of pressures between normal animals and those with mitral stenosis. The average integrated mean pulmonary vein pressure in 44 normal animals was found to be 8.3 ± 2.6 mm. Hg. Twenty-nine catheterizations in animals with experimental mitral stenosis revealed pulmonary vein pressures in excess of 15 mm. Hg. In 16 of the 29 instances, the pulmonary vein pressures were in excess of 20 mm. Hg. It is important to note that dogs with pulmonary vein pressures above 25 mm. Hg did not survive for extended periods of time because of intervention of pulmonary edema. It is also important to note that a number of animals, not presented, died of pulmonary edema after operation, and death occurred before catheterization was possible.

TABLE II. DIFFERENCE IN FREQUENCY OF DISTRIBUTION OF PULMONARY VASCULAR PRESSURES IN NORMAL ANIMALS AND ANIMALS WITH MITRAL STENOSIS

PULMONARY VEIN PRESSURE MM. Hg	NUMBER OF CATHETERIZATIONS		MEAN PULMONARY ARTERY PRESSURE			
			NORMAL		MITRAL STENOSIS	
	NORMAL	MITRAL STENOSIS	MM. Hg	RANGE	MM. Hg	RANGE
0-5	2	0	16.5	(15.4-17.6)		
5-10	32	5	18.2	(12.5-24.3)	16.6	(14.5-20.1)
10-15	10	7	20.9	(17.8-25.4)	21.5	(16.9-24.0)
15-20	0	13			25.0	(21.0-30.2)
20-25	0	10			27.8	(23.1-33.0)
25-30	0	5			32.8	(28.4-35.9)
30-35	0	1			38.9	
Total	44	41				
Av. ±			18.8 ± 2.9			

It is important to note the relationship of the pulmonary artery pressure to that of the pulmonary vein. When the pulmonary vein pressure rose, the pulmonary arterial pressures also rose; however, the rise in pulmonary artery pressure was not proportional to the rise in pulmonary vein pressure. In

other words, the pulmonary vascular pressure gradient, that is, pulmonary artery pressure minus the pulmonary vein pressure (ΔP_P), decreased. Table III shows that this inverse relationship between the gradient and the pulmonary vein pressure was significant when subjected to Fisher's t test for comparison of means. Thus elevation of pulmonary vein pressure to 20 mm. Hg or above caused approximately a 50 per cent decrease in ΔP_P.

TABLE III. RELATION OF PULMONARY VASCULAR PRESSURE GRADIENT TO PULMONARY VEIN PRESSURE IN NORMAL ANIMALS AND ANIMALS WITH MITRAL STENOSIS

NUMBER OF CATHETERIZATIONS	PULMONARY VEIN PRESSURE (MM. Hg)	ΔP_P (MM. Hg $\pm \sigma$)
39	Below 10	10.4 ± 3.0*
30	10-20	8.3 ± 2.3*
16	20 and above	5.8 ± 2.6†

Significance: *t = 3.13, P = < 0.01; †t = 3.30, P = < 0.01.

In the human being: Table IV presents the calculated valve areas (after Dexter)[11] and pulmonary artery pressures recorded in 63 patients with mitral stenosis, divided according to the functional classification of the New York Heart Association. It will be noted that symptoms begin at pulmonary artery pressures as low as 20 mm. Hg. Disabling symptoms such as hemoptysis are usually associated with pressures of 35 mm. or above.

TABLE IV. RELATION BETWEEN FUNCTIONAL CAPACITY, MITRAL VALVE AREA, AND PULMONARY ARTERY PRESSURES IN 63 HUMAN BEINGS

CLASS	FUNCTIONAL CAPACITY	MAJOR SYMPTOMS	MITRAL VALVE AREA* (SQ. CM.) (CALCULATED)	MEAN PULMONARY ARTERY PRESSURE (MM. Hg)
I	Virtually unlimited	None	4-2.5	15-20
II	Some limitations	Dyspnea Pulmonary edema	1.3-1.6	20-35
III	Very limited	Hemoptysis	0.6-1.1	35-60
IV	Bed and chair	Recurrent congestive failure	0.4-0.9	45-90

*Adapted from Dexter. (Functional classifications those of the New York Heart Association.)

Comment: From the data just presented, the symptomatology associated with small but definite increases in pulmonary artery pressures in early mitral stenosis can be explained. In early mitral stenosis, high pulmonary vein pressures are associated with a relatively small rise in pulmonary artery pressure. Thus, for example, a patient with a mean pulmonary artery pressure of 25 mm. Hg may have a pulmonary capillary pressure near the colloidal osmotic pressure of plasma. Under these circumstances, sudden increases in flow in response to exercise can readily precipitate acute pulmonary edema from the sudden increase in pulmonary venous pressure to above the normal osmotic pressure of 26 mm. Hg.

Valve Area and Wedge Pressures.—

In the animal: The area of the left auriculoventricular inflow tract before and after surgery for a group of animals was obtained by measuring the mitral ring circumference in the dogs at death and considering this to be the same

as the circumference of the mitral ring before surgery. In the same dogs the circumference of the stenotic area just above the mitral ring was also measured. This was considered to be the postoperative circumference of the inflow tract. From the circumference, the area was calculated.

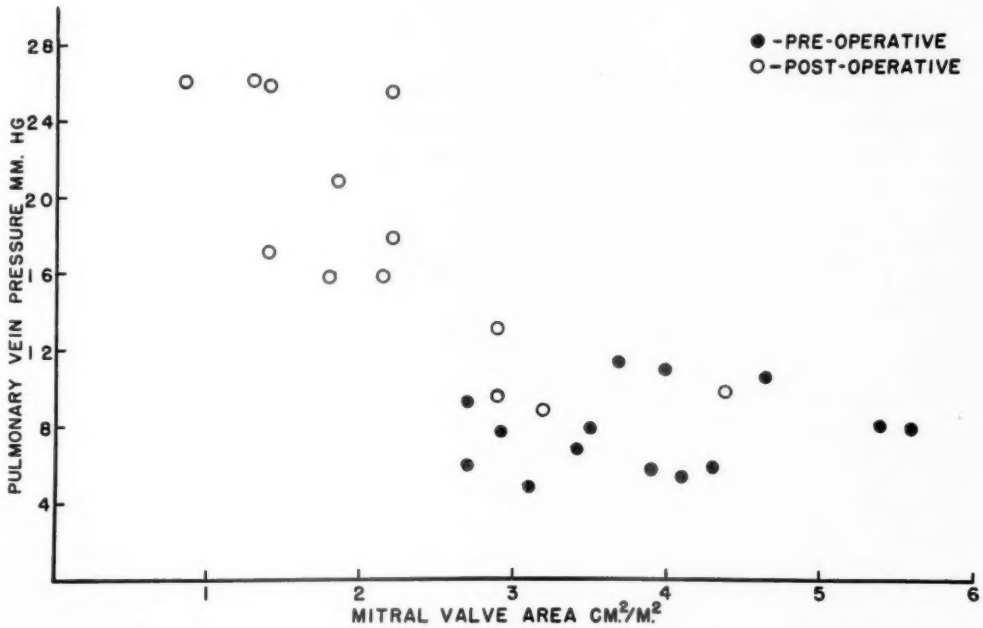

Fig. 1.—Relation between mitral valve area and pulmonary vein pressure in normal dogs and dogs with mitral stenosis. Note that whenever the pulmonary vein pressure exceeded 15 mm. Hg the mitral valve area was smaller than in normal animals. Pressures in excess of 26 mm. Hg were not achieved because of the intervention of pulmonary edema.

As would be predicted, an inverse relationship was found between mitral orifice area and pulmonary vein pressure. Fig. 1 demonstrates that, whenever the pulmonary vein pressure exceeded 15 mm. Hg, the mitral orifice area was smaller than that found in normal animals. It is probable that the constancy of flow in these groups of animals contributed to the high significance of the correlation (see cardiac output studies). It is of note that animals rarely survived with pulmonary vein pressures equal to that of normal osmotic pressure of protein (26 mm. Hg) or with mitral orifice areas of 1 cm.² per square meter because of the occurrence of pulmonary edema. A less constant but yet significant relationship between pulmonary artery pressure and mitral orifice area was also demonstrated. Thus 13 animals with mitral orifice areas below 3 cm.² per square meter had an average pulmonary artery pressure of 24.5 ± 6.6 mm. Hg, whereas 13 animals with orifice areas above 3 cm.² per square meter had a pulmonary artery pressure of 18.4 ± 2.8 mm. Hg. The difference in pressure between these two groups was highly significant ($t = 3.09$, $P < .01$). Using Gorlin's formula, the effective area of the mitral valve orifice was calculated. The resulting figure was plotted against the actual measured area in 23 animals (Fig. 2). All points would fall on the line of identity if the correlation were perfect. However, the figure indicates that large discrepancies are possible in the same animal between actual and

calculated areas. This is especially significant because instead of using the wedge pressure in the calculation, actual pulmonary vein pressure was used. This was done because recent work in our laboratory in dogs has failed to correlate closely the wedge pressure with pulmonary vein pressure when the latter was below about 17 mm. Hg.[12]

In the human being: In six instances satisfactory wedge pressure was obtained both pre- and postoperatively on the same patient (Table V). "Arteriolar" and total pulmonary resistance were calculated. In addition, in two fatal cases, measurement of valve area in the post-mortem specimen, as compared to calculated area, gave the following results: 0.4 actual, 0.9 calculated and 0.1 actual, 0.6 calculated.

TABLE V. VALVE AREA, WEDGE PRESSURE, AND PULMONARY RESISTANCE BEFORE AND AFTER COMMISSUROTOMY

PATIENT	PERIOD	CLASS	CALCULATED MITRAL VALVE AREA	MEAN PRESSURE		RESISTANCE	
				WEDGE	PULMONARY ARTERY	PULMONARY ARTERIOLAR	TOTAL PULMONARY
T. J.	Before	III	0.7	32	66	847	1638
	After	I	2.6	11	25	851	449
L. C.	Before	III	1.1	38	52	230	855
	After	I	1.3	15	22	139	437
T. W.	Before	III	0.9	23	35	238	391
	After	II	1.9	20	35	240	315
P. R.	Before	III	1.1	16	37	485	854
	After	I	2.4	9	30	361	516
M. M.	Before	III	1.1	31	43	178	637
	After	II	1.6	14	26	215	466
M. L.	Before	IV	.3	65	92	884	3019
	After	I	.5	44	49	130	1272
Average	Before	III-IV	.8	34	54	477	1232
	After	I-II	1.7	19	31	223	576
Normal			4-6 cm.	6-12	11-13	67	166

Comment: The pressure changes that occur in the pulmonary vein and, to a lesser extent, in the pulmonary artery in the early stages of mitral stenosis are directly related to the size of the mitral valve, flow being constant. In the animal it was shown that when the valve area is reduced to one-half or less of its normal area, pulmonary vein pressures of 15 mm. or more are obtained. Comparison of these data to those derived from the human being corresponds to a pulmonary artery pressure of 25 mm. Hg (Functional class II), at which level symptoms begin.

Gorlin's formula for the calculation of the effective area of the stenotic mitral valve is theoretically valid. However, the applicability of the formula has been questioned since it depends upon the following assumptions: (1) there is absence of mitral regurgitation, (2) wedge pressures equal left atrial pressures, and (3) cardiac output as measured by the Fick or dye method corresponds to the true flow. In our experience, satisfactory wedge pressures are seldom obtained in those human beings where the mean pulmonary artery pressure is over 60 mm. Hg (see patient, M. L., Table V). Further, experiments in dogs have cast some doubt on the validity of the wedge pressure unless the pulmonary vein pressure is above 17 mm. Hg.[12] In regard to flow

measurements, discrepancies as large as 25 per cent are frequently observed between cardiac output measured simultaneously with the dye and Fick methods.[4] The observations mentioned would make it hazardous in an individual case to predict mitral orifice area by the method of Gorlin. However, both Gorlin's formula and the wedge pressure may be of value when applied to large groups rather than to the individual case.

Cardiac Output Studies.—

In the animal: Fig. 3 shows the relationship of cardiac index, as determined by the direct Fick method, to left ventricular filling pressure in normal dogs and those with mitral stenosis. It will be noted that, in the normal group, an increase in left atrial pressure of approximately 2 mm. Hg was associated with an increase in cardiac output of about 0.8 L. per square meter per minute. Table VI shows that the regular relationship between left atrial pressure and cardiac index is statistically reliable.

TABLE VI. RELATION OF LEFT ATRIAL PRESSURE TO "CARDIAC INDEX" DETERMINED BY THE FICK METHOD IN NORMAL DOGS

NUMBER OF ANIMALS	LEFT ATRIAL PRESSURE (MM. Hg)	CARDIAC INDEX (L./M²/MIN. ±)
16	Below 6	2.8 ± 0.9*
16	6-8.2	4.4 ± 1.0†
17	8.3 and above	5.5 ± 1.2†

Significance: *t = 4.67, P = 0.01; †t = 2.88, P = 0.01.

Since the operated group consisted of animals with varying degrees of stenosis, it can be predicted that this relationship between flow and left atrial pressure would no longer obtain. By segregating the operated animals into two equal groups on the basis of the left atrial pressure, it was found that the mean cardiac index for the low group was 4.4 ± 1.1 L. per square meter per minute, whereas for the high group it was 4.8 ± 1.3 L. per square meter per minute. Calculating the significance of the difference between the two means by application of Fisher's t test, it is found that t = 0.97, P = 0.3 – 0.4, indicating that the values are not significantly different.

The mean cardiac index by the Fick method was 4.2 ± 1.5 L. per square meter per minute in the entire group of normal animals and 4.6 ± 1.2 L. per square meter per minute in the animals with mitral stenosis. Applying Fisher's t test, it was found that the means were not significantly different, t = 1.19 and p = 0.3 – 0.2. The cardiac index was measured by the dye injection technique in 26 normal animals and in 7 animals with mitral stenosis (pulmonary vein pressure above 15 millimeters of mercury). The flow values by this method were 4.4 ± 1.5 and 4.3 ± 0.4 L. per square meter per minute, respectively. Therefore, although the procedure raised left atrial pressure to very high values, the cardiac output as measured remained essentially unchanged in the period studied.

In the human being: Eight class IV patients had an average preoperative cardiac output of 3.07 L. per minute as compared to a predicted normal of 5.85. The cardiac output for all 31 patients was 4.14 preoperatively. Post-

operatively it was 4.15; however, in the class IV patients an increase of 1 L. was obtained postoperatively. This figure is not statistically significant. This is probably due to the small number of cases studied in this group.

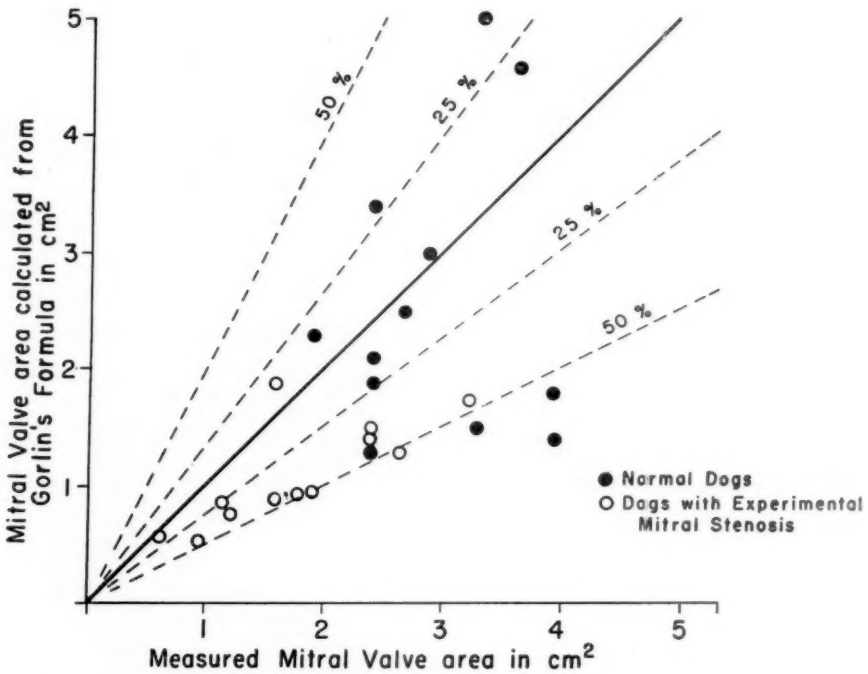

Fig. 2.—Relation between calculated mitral valve area (Gorlin) and actual measured valve area. All points would fall on the line of identity if the correlation were perfect.

Comment: From these data it would appear that in early mitral stenosis the resting cardiac output remains essentially unchanged. In the normal animal the cardiac output is positively correlated with left atrial pressure. As the left ventricular filling pressure was elevated, cardiac output increased, as would be predicted from Starling's law of the heart. Thus, with each increment increase in left atrial pressure of 2 mm. Hg there was an associated rise in output of about 0.8 L. per square meter per minute. These findings again emphasize the importance to cardiodynamics of small pressure changes in the lesser circulation. The absence of a positive correlation between flow and left atrial pressure in animals with mitral stenosis is probably related to the varying degrees of stenosis in this group. The left atrial pressure was, as noted, inversely correlated with the effective mitral valve aperture. Since cardiac output was not altered, one may properly infer that the extra pressure was necessary to overcome the resistance of the stenotic mitral valve. It seems likely that, were one dealing with intraindividual variations with changes in conditions, a positive correlation between flow and left atrial pressure would be found, but at a higher left atrial pressure level.

On the other hand, the finding of lower than normal cardiac output in advanced cases in human beings is likely due to a relatively greater degree of stenosis and to increased pulmonary resistance. After a variable period of time, this sometimes results in failure which further tends to decrease the

cardiac output. The failure to revert completely the resting cardiac output to normal postoperatively in class IV patients is likely due to the following: (1) The condition of the valve is such that complete repair is impossible. (2) Pulmonary vascular resistance does not revert completely to normal (Table V). (3) A degree of myocardial damage may be permanent.

Blood Volume (Total and Central).—

In the animal: In a group of 37 animals, normal and operated upon, central blood volume was calculated according to Stewart's formula.[5] Calculations were made using the cardiac output estimated both by the dye and direct Fick methods. In this group pulmonary vein pressures ranged from 4 to 26 mm. Hg. Animals with pulmonary venous pressures below 15 mm. Hg had pulmonary blood volumes ranging from 250 to 950 c.c. Animals with pressures above 15 mm. Hg had pulmonary blood values ranging from 450 to 1,050 c.c. These values were found to be not significantly different.

In the human being: Table VII presents values for the total blood volume and the central blood volume as determined in 13 cases. The average total blood volume was increased to 5,225 c.c. initially (predicted normal 4,292 c.c.) and fell to 4,835, a probably significant decrease of 390 c.c. ($P = 0.06$). In the 3 class IV patients studied, there was a decrease of approximately 1 L. The average central blood volume was 1,035 c.c., 198 c.c. larger than the predicted normal for the group. This did not change after surgery.

TABLE VII. TOTAL AND CENTRAL BLOOD VOLUME FOR 13 PATIENTS UNDERGOING VALVOTOMY

	CENTRAL BLOOD VOLUME (C.C.)	TOTAL BLOOD VOLUME (C.C.)
Before	1,035	5,225
After	1,001	5,835
Predicted normal	837	4,292

Comment: From these data it might be inferred that there is no change in pulmonary blood volume with mitral stenosis. However, it is to be pointed out that the accuracy of the method of estimation of pulmonary blood volume has been questioned by numerous investigators.[13]

TABLE VIII. RELATION OF PULMONARY VASCULAR RESISTANCE TO PULMONARY VEIN PRESSURE IN NORMAL ANIMALS AND ANIMALS WITH MITRAL STENOSIS

NUMBER OF CATHETERIZATIONS	PULMONARY VEIN PRESSURE (MM. Hg)	PULMONARY VASCULAR RESISTANCE (MM. Hg/L./M^2/MIN./±)
35	0-10	2.43 ± 1.16*
27	10-20	1.79 ± 0.62†
16	20 and above	1.25 ± 0.62†

Significance: *$t = 2.61$, $P = 0.01$; †$t = 2.75$, $P = 0.01$.

Pulmonary Vascular Resistance.—

In the animal: A significant inverse relationship between calculated pulmonary vascular resistance and pulmonary vein pressure was found as indicated in Table VIII. Fig. 4 presents the relationship of pulmonary vascular resistance to pulmonary vein pressure in 6 dogs studied both before and after operation in which pulmonary vein pressure was successfully raised

above 20 mm. Hg by mitral obstruction. A postoperative decrease in calculated resistance was found in each case. The pulmonary artery pressure in these 6 animals averaged 20.2 mm. Hg in the normal state and 29.0 mm. Hg after production of mitral stenosis. An opportunity was had recently to study vascular resistance in a dog with mitral obstruction that has survived for fourteen months (Fig. 5). In spite of the recent presence of ascites, peripheral edema, and elevated right atrial pressure (11.7 mm. Hg), the calculated resistance remained below the preoperative level. This suggests that right ventricular failure can occur before the pulmonary vascular resistance increases due to vascular narrowing.

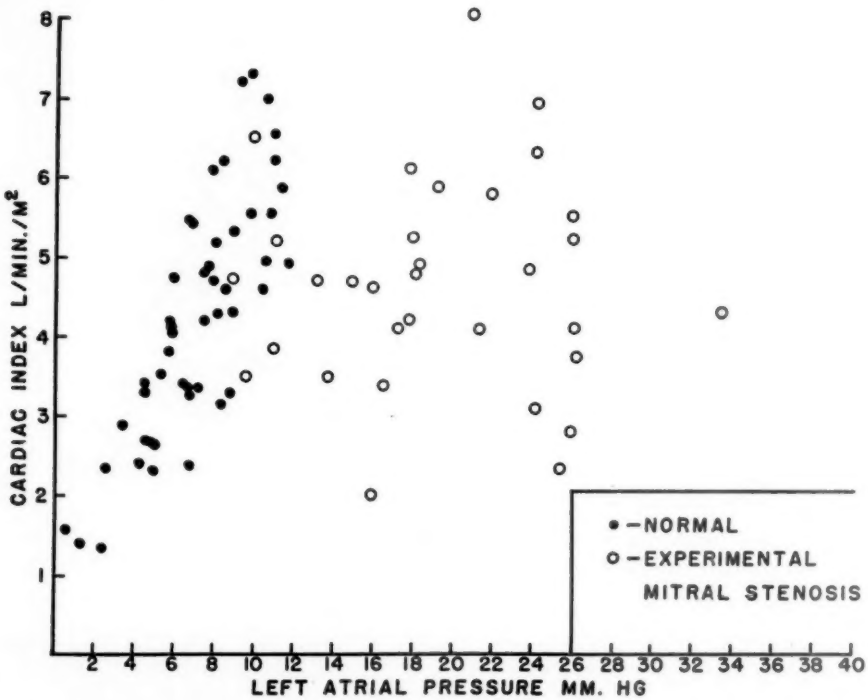

Fig. 3.—Relation between cardiac index measured by the direct Fick method and left atrial pressure in normal dogs and dogs with mitral stenosis. Note that the left ventricular filling pressure was positively correlated with flow in normal dogs. Cardiac index was maintained by virtue of an elevated left atrial pressure in animals with mitral stenosis.

In the human being: In Table V the pre- and postoperative pulmonary resistance is presented in 6 patients on whom wedge pressures were obtained. The finding of high preoperative resistances confirms the findings of others.[11, 14] It will be noted that arteriolar resistance decreased in all but 2 patients. All of these patients were in classes III and IV.

The data reported emphasize the importance of the role of the absolute intraluminal pressure in total resistance in the normal pulmonary vascular bed. Since blood vessels are distensible elastic structures, the intraluminal pressure must be an important determinant of vessels' diameter. Since the volume flow for a given pressure gradient varies with the fourth power of the radius of a tube, it is obvious that this factor can be of great importance. Thus, it seems proper to suggest from the data reported that as pulmonary

vein pressure is elevated the cross-sectional area of the pulmonary vascular bed is probably increased and that, therefore, movement of a given volume of blood is accomplished with a smaller pressure drop.

In mitral stenosis in man, one ordinarily finds elevations in pulmonary artery pressure when the disease is advanced and of long duration. Since changes of comparable magnitude were not observed in dogs over the period of study employed, it is suggested that the pulmonary artery pressure rise is not a passive hydrodynamic phenomenon but rather results from slow chronic (spastic or organic) changes in the blood vessels altering their elastic and/or viscous properties. It is felt that insufficient time has passed for these changes to have taken place in the animals reported. When the changes mentioned occur, the pulmonary vascular resistance rises to high levels.

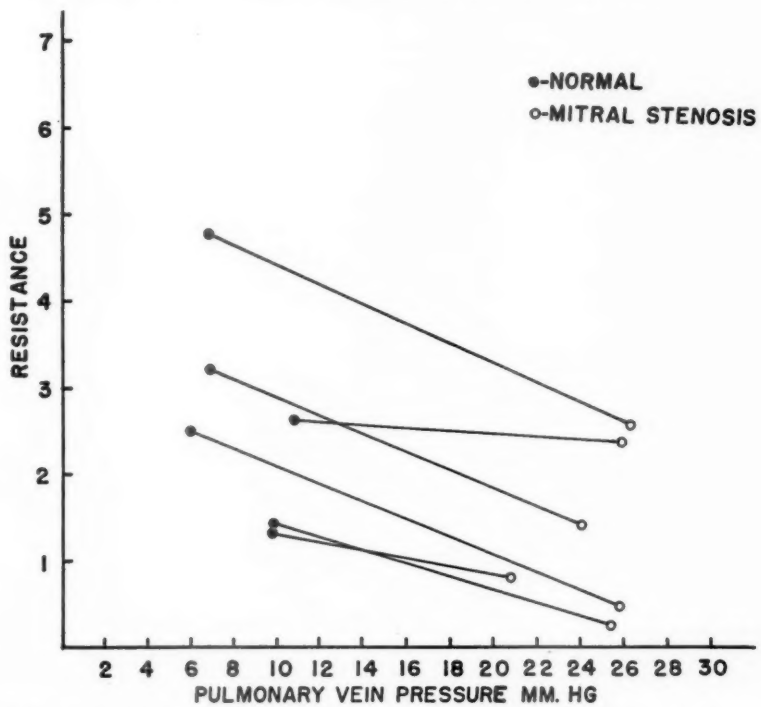

Fig. 4.—Relation between calculated pulmonary vascular resistance in mm. Hg/L./min./m² and pulmonary vein pressure in six dogs studied before and after the production of experimental mitral stenosis. Note the postoperative decrease in resistance in each case.

Lung Biopsy.—

In the animal: The lungs of 50 animals with pulmonary vein hypertension were studied for the presence of arteriosclerosis. These animals lived for varying periods of time up to fourteen months. In only one animal was narrowing of the pulmonary muscular arteries by mild to moderate medial hypertrophy noticed.* This animal lived for fourteen months and died with pulmonary edema. Unfortunately, death occurred before catheterization could be carried out. However, catheterization eleven months previously revealed a pulmonary vein pressure of 24 mm. Hg and autopsy showed a mitral valve diameter of one centimeter.

*Dr. Jesse Edwards was kind enough to review the slide in this animal.

In the human being: In an attempt to evaluate pulmonary pathology found in mitral stenosis,[15, 16] lung biopsies have been studied in 28 of the 31 patients. Seven showed an abnormal degree of arteriosclerosis and 4 of the 7 were in functional class IV. The average pulmonary artery pressure of 61 mm. Hg in the 7 cases was probbaly a significant elevation above the mean of the entire group. Eleven patients had chronic passive congestion and the remaining 10 had no significant changes. Postoperatively, the average pulmonary artery pressure, even in class IV patients, decreased significantly.

Comment: Some class III and IV patients have artery narrowing, others do not; the cause of this phenomenon is unknown. Experiments in dogs indicate that the hypertension is necessary for a period of at least fourteen

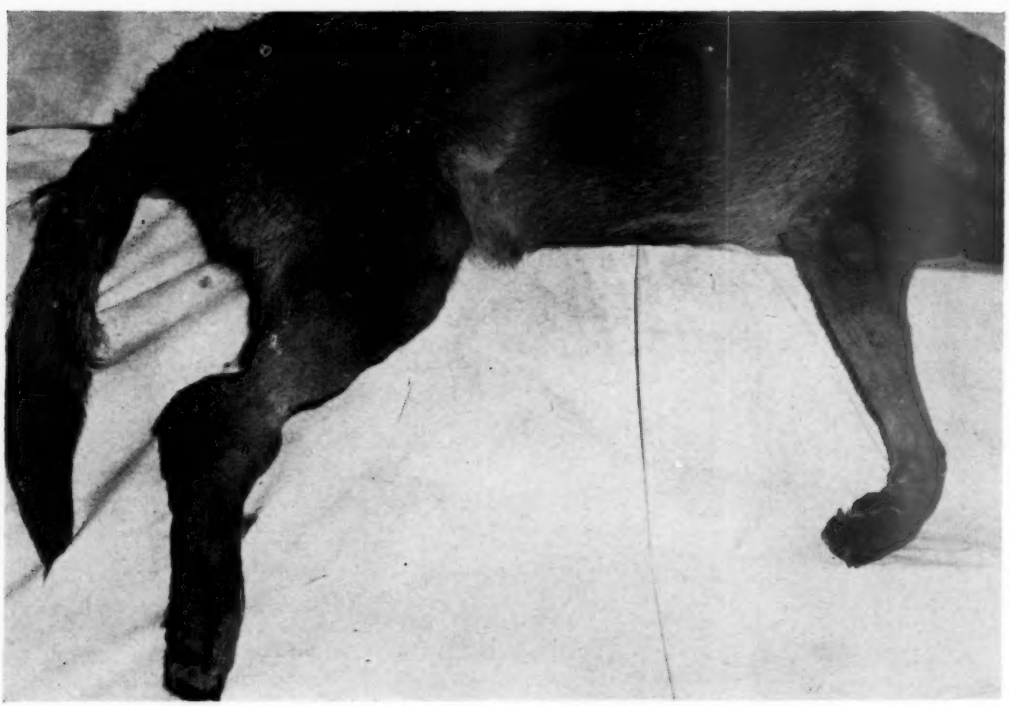

Fig. 5.—A dog with mitral stenosis that has survived for fourteen months. Note the peripheral edema (pitting of the hind leg) that is present. The right atrial pressure was 11.7 mm. Hg. Pulmonary vascular resistance remained below the preoperative level.

months to produce the changes. The presence of these changes in the smaller pulmonary arteries in no way prevents the relief of pulmonary artery hypertension or symptomatic improvement.

Postoperative Pulmonary Artery Pressure Changes.—

In the human being: The fall in mean pulmonary arterial pressure for the 31 individual patients is plotted against the initial level of pulmonary arterial pressure in Fig. 6. A highly significant negative correlation was obtained ($r = -0.8$, $P < .01$).

Comment: Thus, the higher the initial pressure, the greater the fall, and the lower the pressure, the less the fall. A similar correlation has been described by Janton and co-workers.[17] Since the amount of disability is roughly

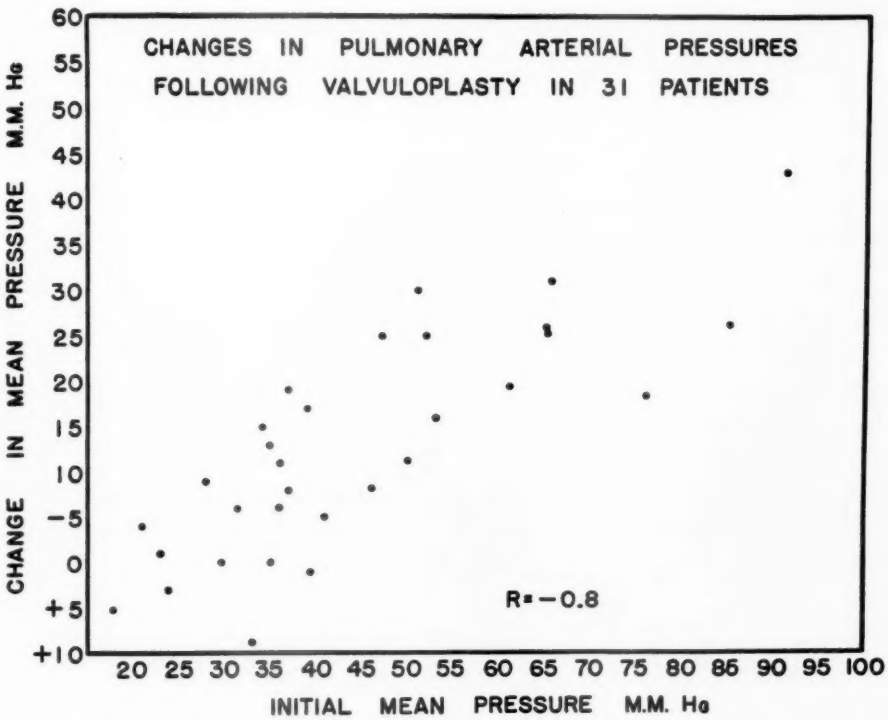
CHANGES IN PULMONARY ARTERIAL PRESSURES
FOLLOWING VALVULOPLASTY IN 31 PATIENTS
CHANGE IN MEAN PRESSURE M.M. Hg
60 55 50 45 40 35 30 25 20 15 10 −5 0 +5 +10
R = −0.8
20 25 30 35 40 45 50 55 60 65 70 75 80 85 90 95 100
INITIAL MEAN PRESSURE M.M. Hg

Fig. 6.—The graph shows changes in the pulmonary arterial pressures following valvotomy in 31 patients. There is a highly significant negative correlation between the changing pressure and the initial pressure in the pulmonary artery.

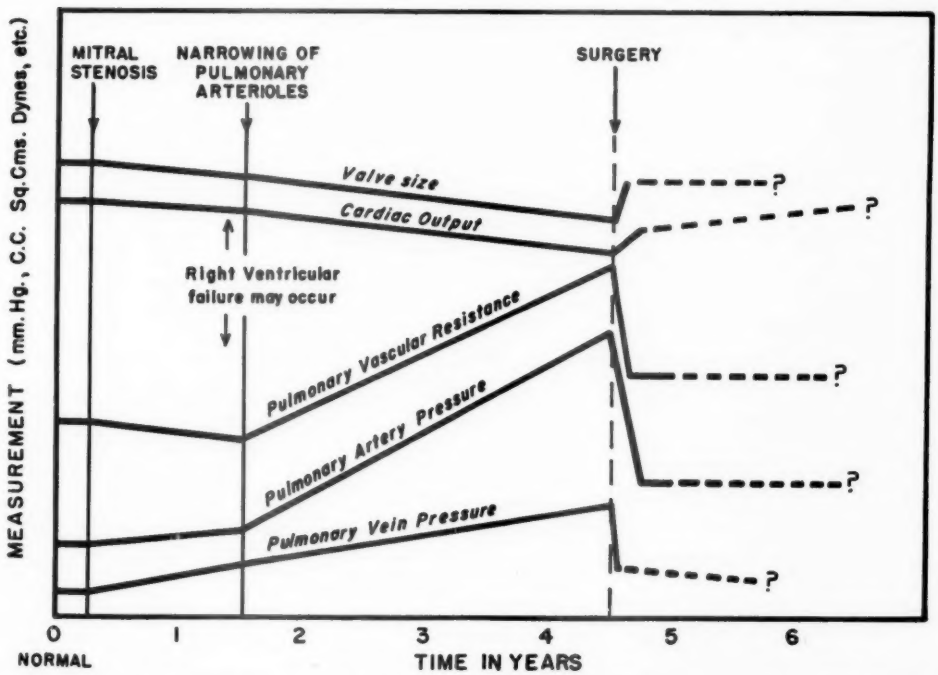

Fig. 7.—Graph showing approximate events occurring in mitral stenosis before and after surgery.

proportional to the degree of pulmonary hypertension, the reduction of pulmonary pressures, in general, is greater in those patients with more advanced symptoms. These results support the contention that pulmonary hypertension is one of the most important criteria for surgery and that valvotomy is effective in lowering high pulmonary pressure. It is also important to note that percentage fall in the low pressure group was approximately the same as that in the high pressure group. This would signify that the hypertension in the pulmonary artery is not fixed.

Lung Volume.—

In the human being: Table IX shows the mean total lung volume for 18 patients. The average total lung volume was 4,475 c.c. This value is 14 per cent smaller than the predicted normal for the group (5,183 c.c.). There was little change postoperatively. The residual volume was 2,027 c.c., a value 28 per cent above the predicted normal for the group (1,579 c.c.). The alveolar nitrogen concentration was 2.23 volumes per cent and did not change.

TABLE IX

	TOTAL LUNG VOLUME	RESIDUAL VOLUME	RATIO OF TOTAL LUNG VOLUME TO RESIDUAL AIR (PER CENT)	ALVEOLAR NITROGEN RETENTION (VOLUME PER CENT)
Before	4,475	2,027	45	2.23
After	4,114	1,879	46	2.36
Predicted normal	5,183	1,579	30	1.14

Comment: These data are slightly different from those of previous workers who report normal or slightly reduced residual volume and a normal alveolar nitrogen concentration in patients with cardiac disease as compared to the normal person. Two of the patients were found to have emphysematous blebs on examination of the lung at surgery, and one had known bronchial asthma. The measurements probably reflect a minimal degree of pulmonary emphysema in some of the patients. The relief of dyspnea experienced by all of these patients cannot be directly related to changes in lung volume or intra-alveolar mixing of gases as measured by this technique.

DISCUSSION

From the previous data, a diagrammatic summary of the approximate hemodynamics of mitral stenosis is presented in Fig. 7. The eventual course of the various individual components following surgery is unknown at the present time. Whether the valve, when cut, remains open and is not affected by recurrence of rheumatic fever is still a moot point. However, it would appear that when surgery is undertaken successfully, the hemodynamics approach normalcy and a corresponding improvement in the patient's status is obtained.

SUMMARY

Experimental and clinical data on mitral stenosis are presented. The studies include pulmonary artery and vein pressures, valve areas, wedge pressures, cardiac outputs, central blood volumes, and pulmonary lung volumes. It

would appear that in the dog with early mitral stenosis, as the pulmonary vein pressure rises, there is also a rise in the pulmonary arterial pressure, but the latter rise is not as great. This results in both a decreased pressure gradient and a lowered pulmonary resistance. Whenever the pulmonary vein pressure exceeded 15 mm. Hg, the mitral orifice was smaller than that found in normal dogs. Left atrial pressure was positively correlated with cardiac output in normal animals. This correlation was not obtained in animals with mitral stenosis, probably a result of varying degrees of stenosis. Pulmonary edema was positively correlated with pulmonary vein pressure in animals. Pulmonary blood volume did not change appreciably in the dog following the production of mitral stenosis. The approximate time interval for pulmonary arteriolar changes to occur following mitral stenosis would appear to be one and one half years in the dog; however, right heart failure can occur before this.

Clinical studies on symptomatic patients usually represent the late stages of mitral stenosis. In the human being with stenosis, pulmonary artery and wedge pressure are elevated, as is the pulmonary arteriolar resistance. Cardiac outputs in the resting state do not change significantly from the normal except in the very late stages. Postoperatively, most abnormal findings approximate normal. The pulmonary blood volume was found not to change following surgery, whereas the peripheral blood volume did.

Pathologic changes in the pulmonary arterioles did not prevent a significant drop in pulmonary arterial pressure following surgery. A highly significant negative correlation was obtained between the change in pulmonary arterial pressure and the preoperative mean pressure.

Acknowledgment.—Generous aid by Dr. Maurice B. Visscher and Dr. Richard V. Ebert during the conduct of this study is gratefully acknowledged.

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DISCUSSION

DR. GEORGE H. A. CLOWES, Jr. (Cleveland, Ohio).—The results presented by Dr. Baronofsky and his associates are very interesting, and I wish to congratulate them on this excellent piece of work.

Two years ago we successfully created experimental mitral stenosis in dogs. Those animals were used to study the relationship of "wedge pressure" to left auricular pressure during normal respiration with the chest wall intact. This was done by suturing into a pulmonary vein a plastic tube to permit the introduction of a catheter into the left auricle. There was some variance between the wedge pressures and the left auricular pressures observed, particularly at the extremes of high or low pressure. The average mean wedge pressure was found to be 3 mm. Hg below that in the left auricle. Why this was so, we are unable to explain.

In an attempt to shed more light on this problem, we have tried several times to obtain simultaneous recordings of left auricular pressures and wedge pressures in man during thoracotomy. This was accomplished in two patients undergoing mitral commissurotomy. In both instances the mean pressures in the "pulmonary capillary" and left auricle were equal.

Gorlin's formula for the calculation of the area of the mitral orifice has not worked out in our hands. Although this may be due to errors in recording wedge pressures or cardiac outputs, as suggested by Dr. Baronofsky, there has been poor correlation of calculated area to that found in our patients or experimental animals.

CHANGES IN THE PULMONARY VESSELS PRODUCED BY EXPERIMENTAL PULMONARY HYPERTENSION

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MEDIAL hypertrophy and intimal fibrosis in the pulmonary vascular bed may be associated with a variety of congenital cardiovascular deformities, such as the Eisenmenger complex, the atypical or reversed patent ductus arteriosus, the single ventricle, the large interatrial septal defect, and large ventricular defects.[1-4] Similar changes also appear in certain acquired cardiovascular diseases. In each of these cardiac abnormalities, pulmonary hypertension and/or excessive pulmonary blood flow is present. There has been much controversy as to the etiology of the medial hypertrophy and intimal fibrosis which occur in these cases. A number of authors have postulated that pulmonary vascular changes are an additional congenital defect. In recent work,[2, 5, 6] however, evidence has been presented to show that they are not congenital but are the result of long-standing pulmonary hypertension with or without excessive pulmonary blood flow. This study was designed to show the effect of pulmonary hypertension and/or increased pulmonary blood flow on the pulmonary vascular bed and to permit serial microscopic study of the changes produced in the small muscular pulmonary arteries and veins of experimental animals.

METHODS

The study was divided into three parts:

1. *Anastomosis Between the Distal End of the Left Pulmonary Artery and the Side of the Aorta.*—Twenty-one mongrel dogs were used in this group. The procedure produces a large communication between the left pulmonary and systemic circulations with resulting pulmonary hypertension of the left lung and creates a situation somewhat similar to the hemodynamics found in certain patients with congenital heart disease. Preoperative medication of morphine and atropine was given, and endotracheal ether was administered with an intermittent positive pressure apparatus. The animal was placed on its right side, and under sterile conditions an incision was made along the entire length of the fifth left intercostal space. The left pulmonary artery was freed throughout its entire length, and a 3 cm. portion of the aorta was freed just distal to the left subclavian artery. The adventitia was carefully removed from the area in which the anastomosis was to be performed. The

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left pulmonary artery was ligated adjacent to the main pulmonary artery and occluded distally with a rubber-shod bulldog clamp. A tangential portion of the aorta was grasped in a Potts ductus clamp and a longitudinal incision was made in the aorta. A continuous everting type of mattress suture was used to carry out an anastomosis between the end of the left pulmonary artery and the side of the aorta (Fig. 1). The anastomosis was made as large as was technically possible. A large number of the animals initially operated upon died of cardiac failure soon after the anastomosis was opened or within the first week after operation. In spite of this high mortality rate, we continued to make the anastomosis as large as possible because we felt that pressure in the pulmonary vascular system approaching the one in the aorta was necessary

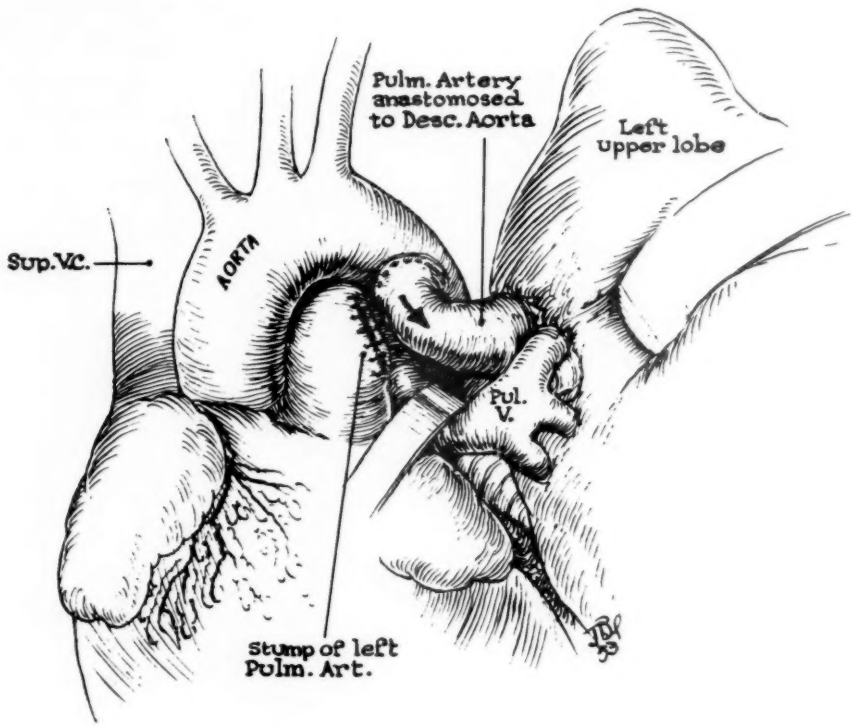


Fig. 1.—Drawing of the procedure used in Group I. The distal end of the left pulmonary artery has been anastomosed to the side of the aorta.

to produce these changes. The administration of digitalis preoperatively seemed to lower the mortality rate. Pressures were taken as far distal in the pulmonary artery as possible and were found to approach those in the aorta (Fig. 2). The chest was closed with silk.

2. *Anastomosis Between the Left Subclavian Artery and the Distal End of the Superior Lobe Pulmonary Vein.*—This portion of the experiment was stimulated by the work of Hahn and Kim [11] in which they demonstrated marked arterialization of the small myocardial veins in dogs that had an anastomosis between the systemic circulation and the coronary sinus. The chest was opened as it was in the previously described procedure, and an anastomosis was carried out between the proximal end of the left subclavian artery and the distal end of

the left superior pulmonary vein (Fig. 3). It was thought that a continuous pulsatile force on the pulmonary veins might cause changes in them similar to those seen when severe mitral regurgitation is present. One of the four animals upon which the procedure was performed died eight hours after the procedure and was found to have a hemorrhagic upper lobe.

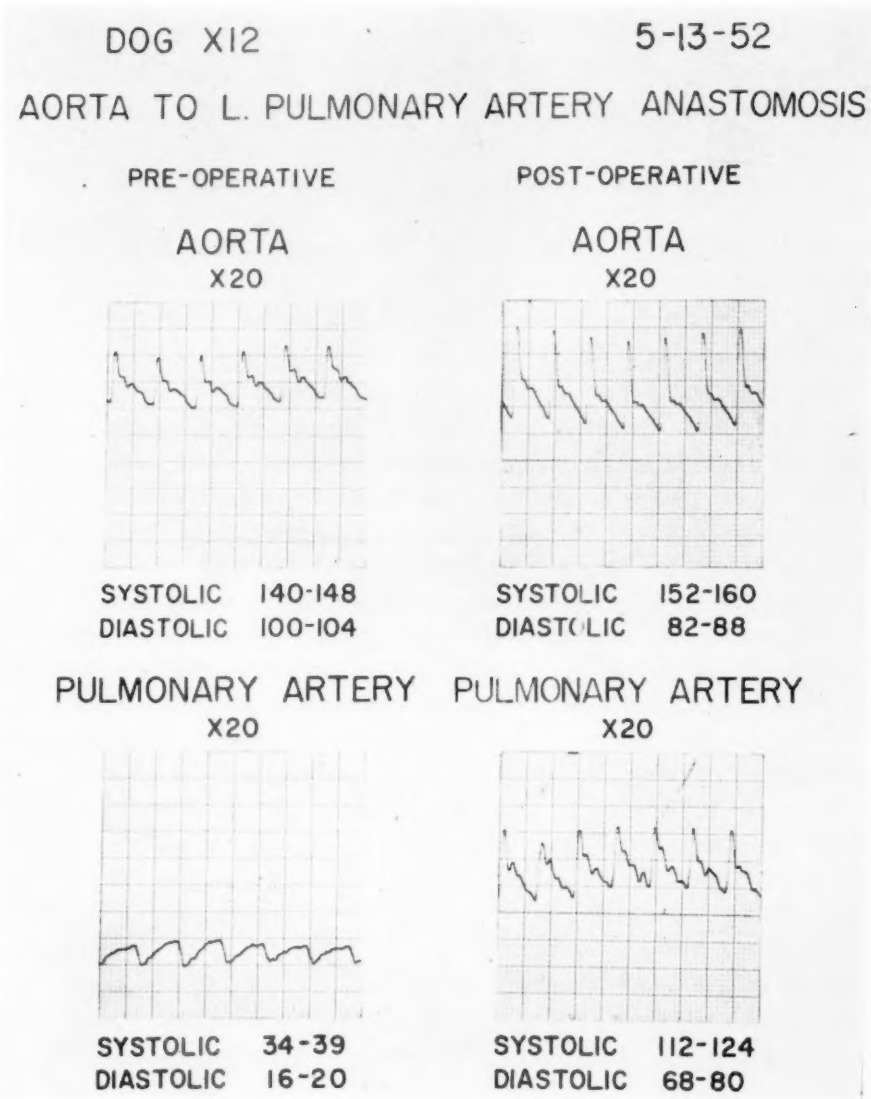


Fig. 2.—Photograph of pressure tracings from the aorta and pulmonary artery of dog before and after the left pulmonary artery was anastomosed to the side of the aorta. The pressure in the pulmonary artery is only slightly lower than that in the aorta.

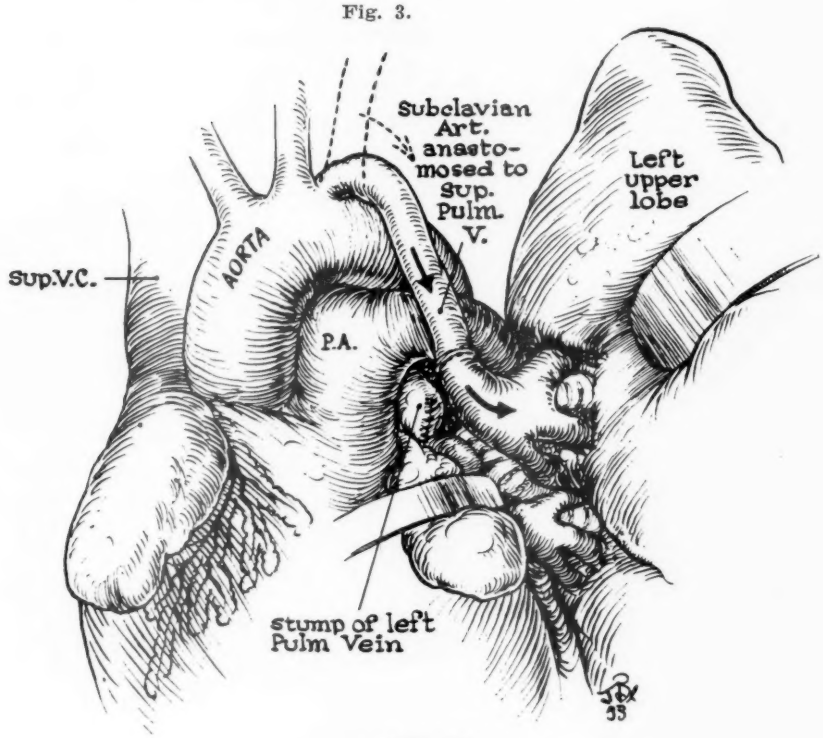
3. *Reversal of Blood Flow Through the Left Upper Lobes.*—In this experiment the proximal pulmonary artery was anastomosed to the distal pulmonary vein, and the distal pulmonary artery was anastomosed to the proximal pulmonary vein. The lower lobes were excised. Thus, the blood flow through the upper lobes of the lungs was reversed. This procedure was performed on three dogs. The left side of the chest was opened as in the previous

experiments, and the left pulmonary artery was dissected free throughout its entire length. The left superior pulmonary vein was likewise dissected free for a considerable distance on the wall of the left auricle. Potts ductus clamps were placed proximally and distally on these structures. They were divided, and anastomoses were carried out with continuous everting sutures of 00000 arterial silk (Fig. 4). In one animal an attempt was made to reverse the circulation in the entire left lung, but the large cuff of left auricle necessary to contain the entire pulmonary venous drainage was so disproportionate with the left pulmonary artery that a satisfactory anastomosis could not be carried out. This animal died several hours after the operation.

RESULTS

Group I.—Only five out of twenty-one dogs survived the procedure beyond one week after the operation. The others died of cardiac failure either immediately after the anastomosis was opened or in the early postoperative period. The administration of digitalis aided in controlling cardiac failure in the animals which survived. The size of the anastomosis was estimated at operation and compared with the animal's postoperative course. In general, the dogs with large anastomoses were much less active, ate porely, gained less weight, developed poorly, and had cardiac failure which was difficult to control by medical means. Those with small anastomoses were very active, often more active than normal dogs; they ate ravenously, and cardiac failure tended to develop in them to a lesser degree than in those with large anastomoses. Biopsies of the lung were performed approximately eight months and one year after operation. Three of the surviving animals have not been sacrificed because we are interested in demonstrating whether or not pulmonary vascular changes are reversible, and we hope that at a later date the left pulmonary artery can be reanastomosed back to the main pulmonary artery in order to see if repression of changes will take place. The studies reported were made on specimens taken from the lungs approximately one year after operation. Biopsy material from the left lung was compared with that taken before operation and with that taken from the right lung. The degree of change depended directly upon the size of the anastomosis. Most of the small and medium muscular arteries showed luminal narrowing due to medial hypertrophy and some showed intimal proliferation as well (Fig. 5). At least ten of the arteries in each section were measured microscopically, and the ratio between the thickness of the wall and the size of the lumen was determined. The ratios corresponded to the general impression gained from observation of the arteries. In the biopsy material taken from the left lung one year after operation, this ratio was found to be far less than before operation. Changes also occurred in the right lung and seemed to be definitely related to the degree of left-sided heart failure. The changes in the right lung consisted primarily of thickening of the walls of both veins and arteries, but were much more marked in the veins (Fig. 6). This finding is similar to that found in patients with chronic left-sided heart failure. One dog in extreme failure died during the final lung biopsy. Post-mortem examination revealed marked

Fig. 3.



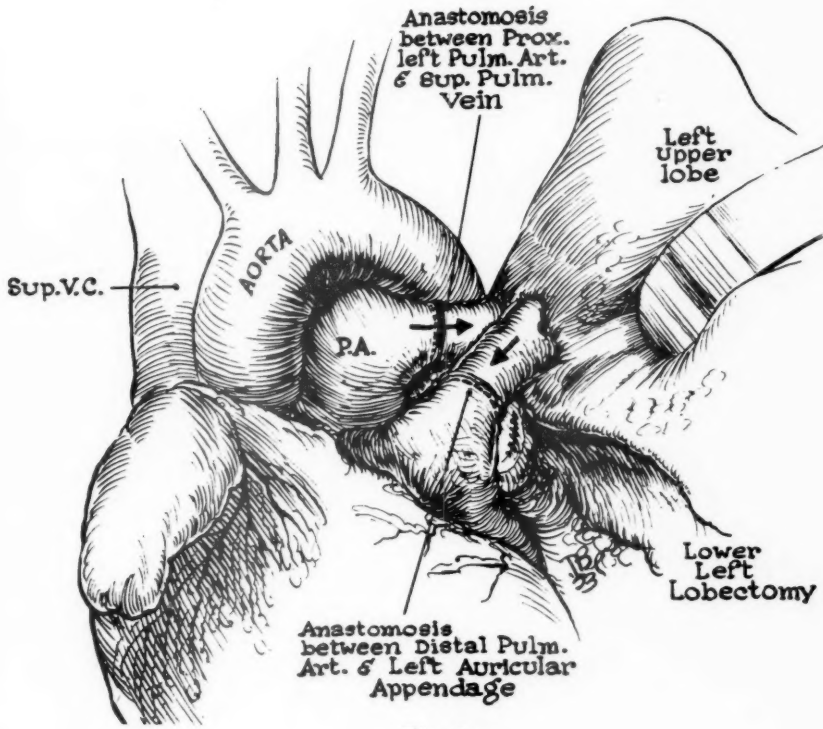

Anastomosis between Prox. left Pulm. Art. & Sup. Pulm. Vein
Left upper lobe
Sup.V.C.
AORTA
P.A.
Lower Left Lobectomy
Anastomosis between Distal Pulm. Art. & Left Auricular Appendage

Fig. 4.

Fig. 3.—Drawing of procedure used in Group II. The left subclavian artery has been anastomosed to the distal end of the superior pulmonary vein. The pulmonary artery is intact.

Fig. 4.—Drawing of the procedure used to reverse the circulation in the lung (Group III). The proximal end of the left pulmonary artery is anastomosed to the distal end of the superior pulmonary vein. The distal end of the left pulmonary artery is anastomosed to the left auricular appendage. The lower lobes have been excised.

left ventricular and auricular hypertrophy and dilatation (Fig. 7). The diameter of the anastomosis was 8 millimeters. Changes were more marked in the pulmonary arteries of this animal than in any other. The animal whose

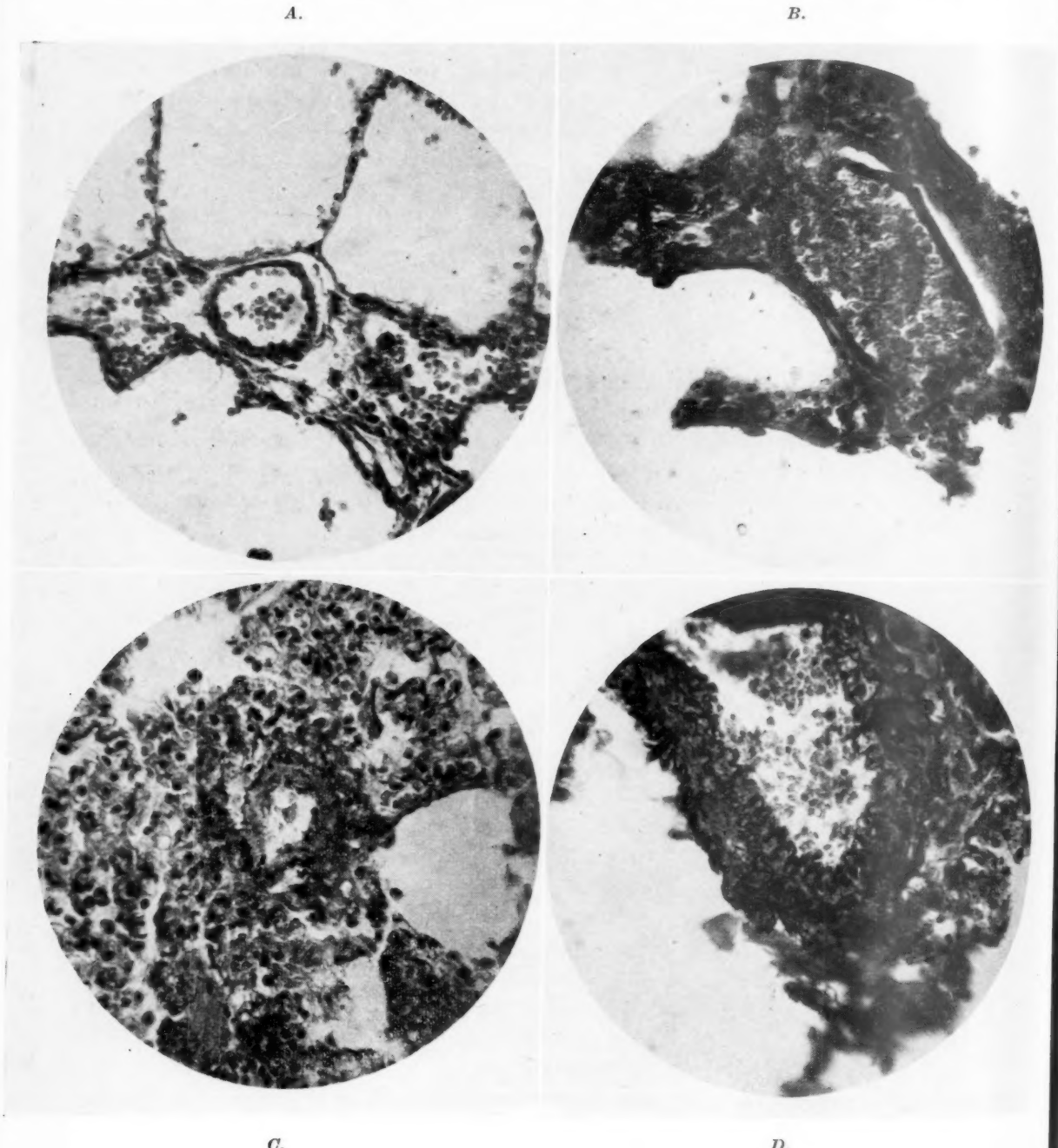
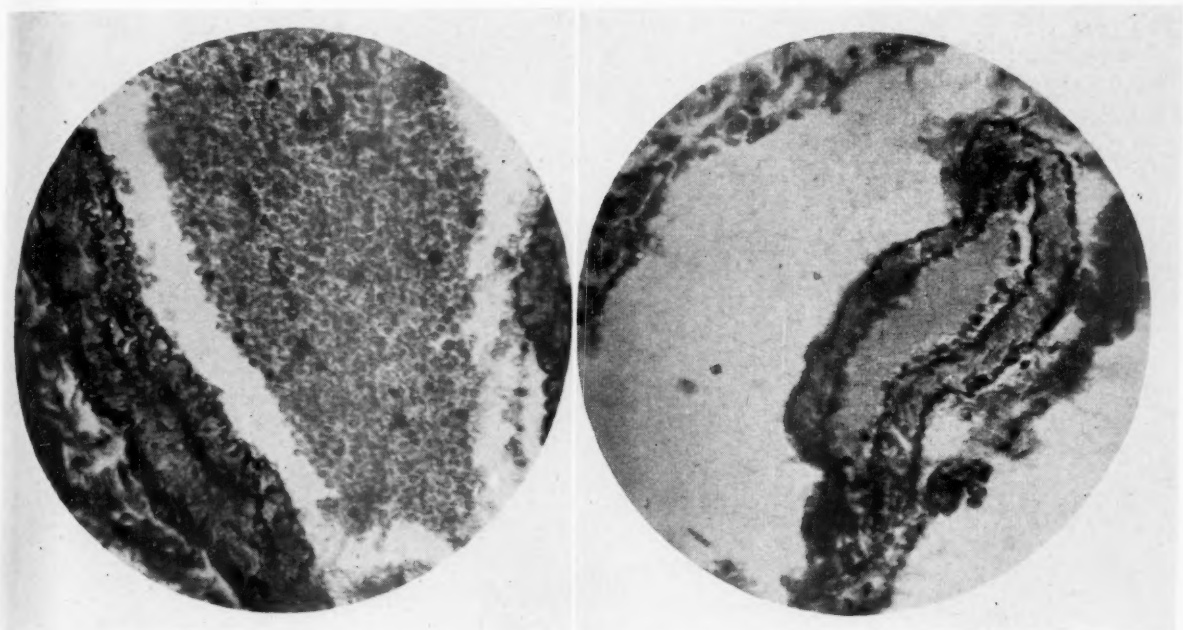


Fig. 5, *A-D.*—*A* and *B*, Photomicrographs of normal small and medium arteries from left lung of dog before operation. *C*, *D*, and *E*, Photomicrographs of small, medium, and large arteries from left lung of dog approximately one year after a large anastomosis was made between the end of the left pulmonary artery and side of the aorta. There is marked medial hypertrophy and moderate proliferation of the intima in these vessels. *F*, Photomicrograph of medium muscular pulmonary artery from lung of dog on which a moderate-sized anastomosis between end of left pulmonary artery and side of aorta had been carried out. There is moderate medial hypertrophy in the wall of this vessel.

lungs showed the least changes was sacrificed (Fig. 8), and the anastomosis measured 2 millimeters. There was little hypertrophy of the left ventricle in this animal (Fig. 8, *B* and *C*). The dog had required less digitalis than the others, was very active, and gained weight well.

Group II.—Three animals survived the procedure. After the immediate postoperative period, their general course was like that of normal dogs. One died during the final lung biopsy, and it was found that the anastomosis had closed even though it had been large at the end of the initial procedure. The most striking changes were in the veins where luminal narrowing and thickening of the walls were present. The thickening was due to medial hypertrophy and marked intimal proliferation. The arteries showed relatively little change. Biopsy material of the lung showed no changes in the arteries and only minimal changes in the veins.



E. *F.*

Fig. 5, *E* and *F*. (*For legend see opposite page.*)

Group III.—One of these animals died in the immediate postoperative period. Biopsy material of the lung in the surviving animals showed no changes in the arteries and only minimal changes in the veins.

DISCUSSION

The first experimental studies carried out on the problem of pulmonary hypertension were by Levy and Blalock[7] in 1939. They anastomosed the proximal end of the left subclavian to the distal end of the left pulmonary artery in twelve dogs, five of which survived. Examination of the lung approximately six months after operation showed the histologic structure of both lungs to be

normal. Injecting the pulmonary vascular bed with an opaque mass likewise showed no deformity. There are several reasons which may account for the absence of changes in the small arteries of these animals. First, mature adult dogs were used. Although there is no conclusive evidence that vascular changes will occur more rapidly in younger animals, in the human being, at least, luminal narrowing and thickening of the walls of the small pulmonary arteries exist normally at birth and continue for several months into infancy.[2,6] If this same sequence of events occurs in the dog and pulmonary hypertension could be created before the luminal narrowing and thickening of the wall entirely disappeared, a rapid and more extreme progression of changes might be produced. Second, the subclavian artery was used, thus the size of the anastomosis that it was possible to perform was limited. Also, the length of the subclavian artery offers some resistance to blood flow. Finally the lung was

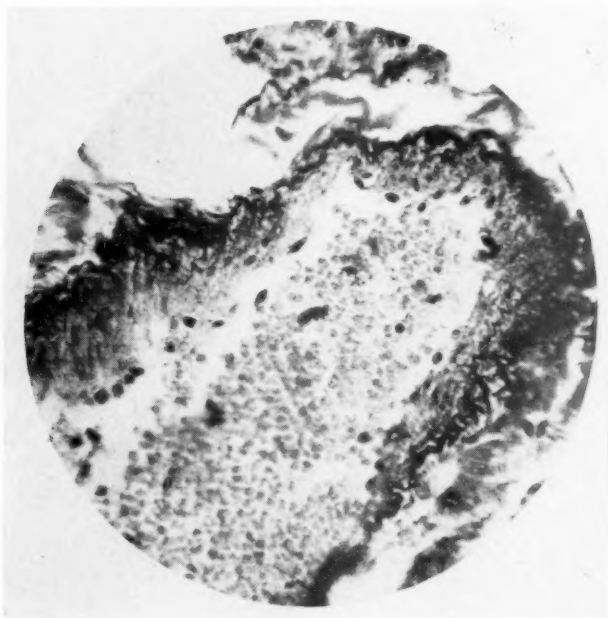
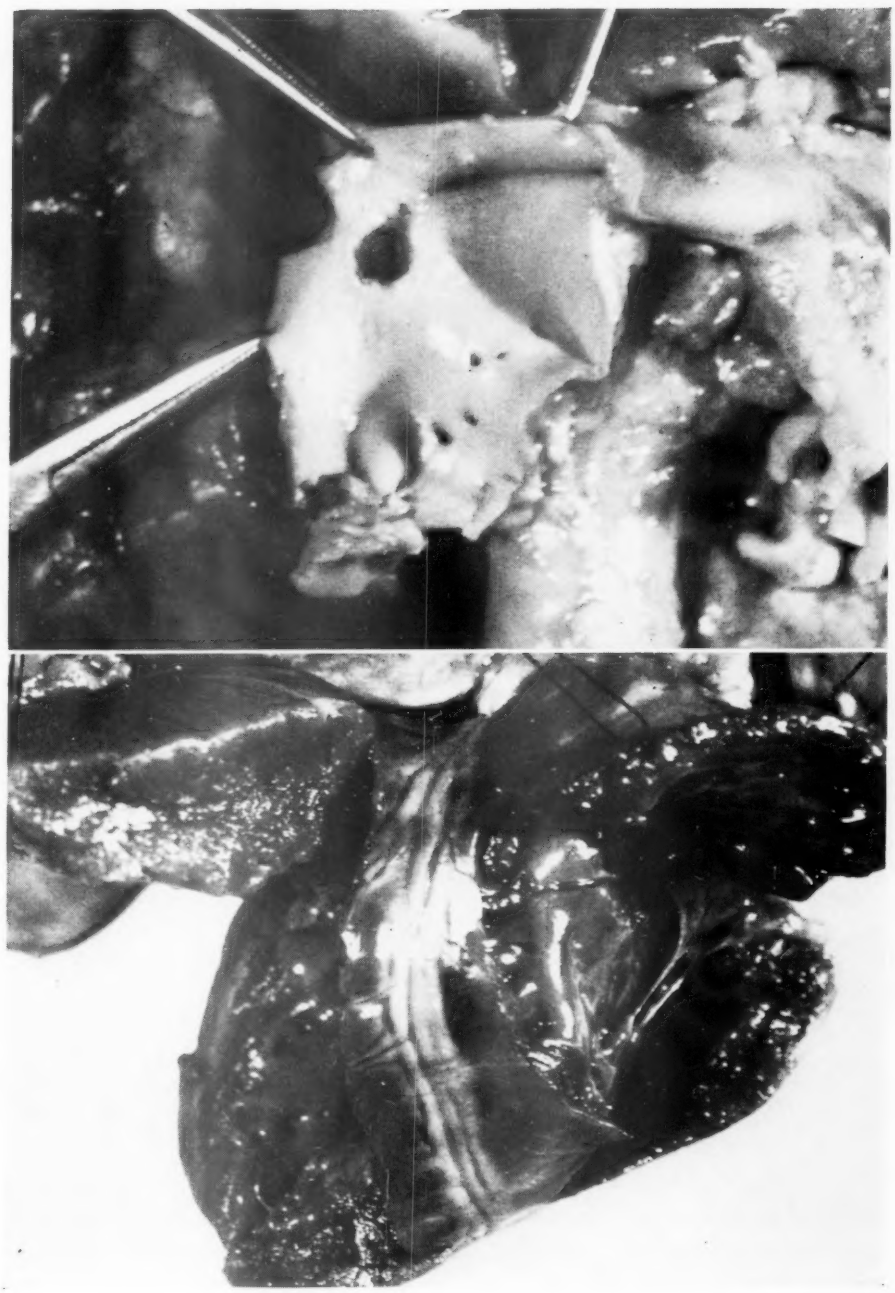


Fig. 6.—Photomicrograph of wall of medium pulmonary vein from right lung of dog approximately one year after a large anastomosis was made between the end of the left pulmonary artery and side of the aorta. There is dilatation and marked intimal proliferation.

examined at approximately six months after operation, which may not have been a long enough period to allow the development of pulmonary vascular changes and pulmonary hypertension. Recently Kawakami[8] produced narrowing of the pulmonary arteries in castrated rabbits by giving daily injections of adrenalin for long periods of time. These changes consisted of both intimal and medial thickening. However, no mention of pulmonary hypertension was made. He noted that the greatest changes occurred at the bifurcation of arteries. Potts and Riker[9] studied the growth of aortic pulmonary anastomoses in pigs. They made 6 mm. incisions in the aorta and pulmonary artery and performed a side-to-side anastomosis. Microscopic examination of the lungs at the end of nine months showed them to be normal. In one pig in

which the actual opening of the anastomosis was 8 mm., it was noted that there was pulmonary artery sclerosis. A comparable anastomosis in a dog on the basis of the body weight of the two animals would be very small, because the pig in this instance weighed 240 pounds.

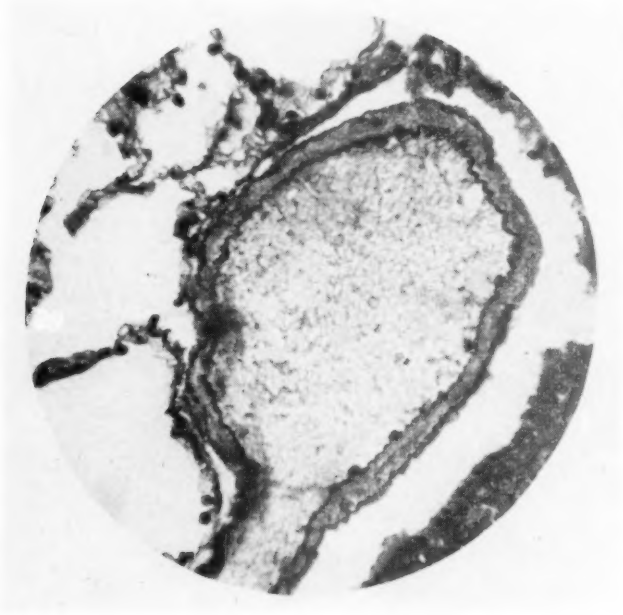
A.



B.

Fig. 7.—*A*, Photograph from aortic side of anastomosis between end of left pulmonary artery and side of aorta. The anastomosis measured 8 mm. in diameter. *B*, Photograph of heart from same animal. Note marked left ventricular hypertrophy and dilatation.

In the present experiment, anastomoses were made as large as technically possible even though a high mortality rate was expected and occurred. Such an anastomosis simulates as closely as possible some of the large communications between the systemic and pulmonary circulations found in patients with certain types of congenital heart disease, such as the atypical patent ductus arteriosus, the Eisenmenger complex, and large ventricular defects. We considered creating large ventricular defects, but the procedure for producing them is more difficult than the procedure which we used. Also, Griffin and Essex[10] pointed out that ventricular septal defects larger than 1 cm. are accompanied by an extremely high mortality rate and that defects smaller than 1 cm. tend to close. An additional advantage of the procedure used in this experiment is that only one lung is affected. Therefore, a larger volume of blood can be shunted through one lung, and the opposite lung serves to some extent as a control. The reasons for using puppies have already been stated. Experimental evidence indicates that the anastomosis would become larger as the dogs increased in size.



A.

Fig. 8, A.—Photomicrograph of medium artery from lung of dog with small anastomosis between end of the left pulmonary artery and side of the aorta. There is no luminal narrowing and only very slight medial hypertrophy.

The changes in the small muscular pulmonary arteries were surprisingly similar to those found in patients with pulmonary hypertension. Most of these vessels showed medial hypertrophy, and some showed intimal fibrosis and proliferation. The degree of these changes seemed to be directly proportional to the size of the anastomosis and, therefore, to the degree of pulmonary hypertension and blood flow. The mechanism of these changes is not understood.

The possibility of a pressor substance or of some neurogenic mechanism must be considered. Although a periarterial neurectomy was performed when the left pulmonary artery was divided, many nerves were still present along the

Fig. 8, *B*.

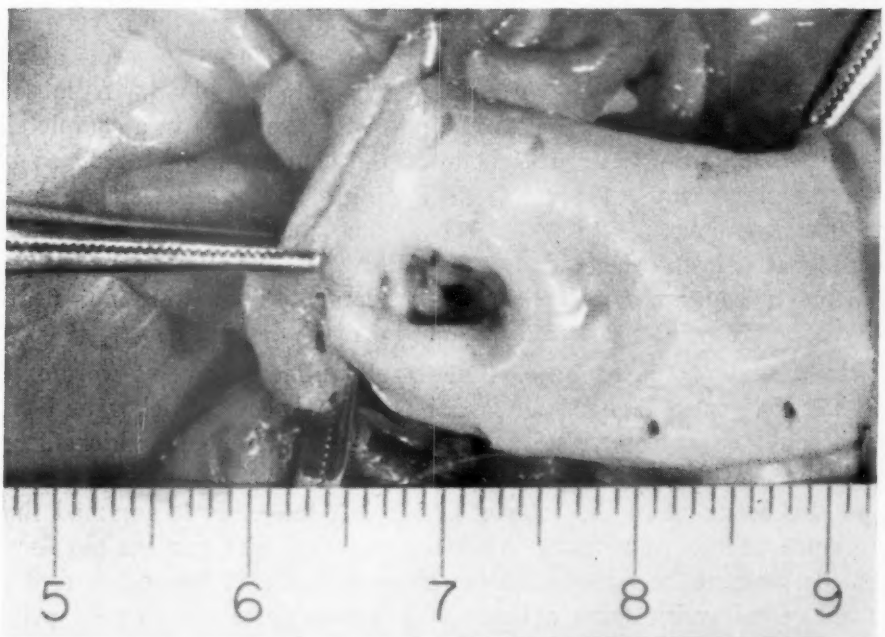


Fig. 8, *C*.

Fig. 8, *B*.—Anastomosis between end of left pulmonary artery and side of aorta photographed from aortic side. The anastomosis measured only 2 mm. in diameter.

Fig. 8, *C*.—Photograph of heart from same animal. Only moderate hypertrophy of the left ventricle is present.

bronchus, in bronchial vessels, and in other regions throughout the pulmonary hilus. The only conclusion that can be drawn is that there is a definite relationship between pressure, blood flow, and pulmonary arterial thickening. It is intended, if possible, to close the aortic-pulmonary anastomosis and reanastomose the left pulmonary artery to the main pulmonary artery at a subsequent date in order to see if these changes regress. At that time the oxygen saturation of blood in the left pulmonary veins will be measured to see if a lung in which such changes are present will fully oxygenate the blood. A subsequent study is also planned to see if similar changes will take place in a completely denervated lung. Mention might be made of the changes which occurred in the vessels of the right lung. There was thickening of the vessel wall and narrowing of the lumen, particularly of the veins. These changes are similar to those in patients with chronic left-sided heart failure and were presumably present for the same reason in our experimental animals. They were not nearly so marked when left-sided heart failure was minimal or absent.

In the second group, changes in the small pulmonary veins were expected since it has long been known that veins tend to become thicker and smaller when subjected to arterial pressures. Although the medial thickening and marked intimal proliferation occur primarily in the veins, minimal changes of this type also occurred in the arteries of the left lung. It is assumed that the high pressure in the pulmonary venous circulation was responsible for these changes. In the sections studied from these animals, it was often difficult to differentiate small veins from arteries and it was necessary to rely primarily on the presence of muscle cells in the media and a deeper pink staining of media in the veins. The interna elastica is absent or incompletely formed in the veins.

In Group III only minimal thickening occurred in the veins, and the arteries appeared normal. Again this can be explained by the relatively low pressure in the pulmonary venous circulation which occurred when the pulmonary blood flow was reversed.

One can, therefore, conclude from this study that luminal narrowing and thickening of the vessel wall due to medial hypertrophy and intimal fibrosis will occur in the small pulmonary blood vessels of animals subjected to a marked increase in pressure in the pulmonary circulation.

SUMMARY

A series of experiments was performed in an attempt to produce changes in the pulmonary vascular system similar to those seen in patients with pulmonary hypertension. In the first group, a large anastomosis between the end of the left pulmonary artery and the side of the aorta was carried out. In the second, an anastomosis between the left subclavian and distal end of the left superior pulmonary vein was performed; and in the third, reversal of the circulation through the upper lobes of the left lung was induced. In the first group, luminal narrowing due to medial hypertrophy and intimal proliferation occurred in the small muscular pulmonary arteries in the lungs of the dogs which survived,

The degree of change seemed to be directly proportional to the size of the anastomosis, the amount of left ventricular hypertrophy, and the degree of pulmonary hypertension. In the second group, there was thickening, particularly of the pulmonary veins and, to a lesser degree, of the small pulmonary arteries. In the third group, thickening of the pulmonary veins occurred to a minimal degree. It is concluded that, in these experimental animals, luminal narrowing due to thickening of the walls of the small pulmonary blood vessels is the result of pulmonary hypertension and excessive blood flow.

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CERTAIN PHYSIOLOGIC, PATHOLOGIC, AND SURGICAL FEATURES OF COMPLETE TRANSPOSITION OF THE GREAT VESSELS

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COMPLETE transposition of the aorta and pulmonary artery is a congenital malformation of the cyanotic variety which, because of its frequency and gravity, constitutes one of the most challenging problems currently facing cardiac surgeons.

With the exception of Blalock and his associates,[1-3] it appears that surgeons have been generally discouraged both by the technical problems involved and the desperately ill status of most of these infants.

It is our purpose and hope that by this candid exposition of our initial researches, mostly failures, we may arouse greater interest among other surgeons in this potentially correctable malformation which is at present the most frequent anatomic type of cyanotic heart disease found at autopsy in infants.

TERMINOLOGY

*Complete Transposition of the Aorta and Pulmonary Artery.** In complete transposition of the great vessels, the aorta arises from the ventricle receiving the sytemic venous blood, and the pulmonary artery originates from the ventricle receiving the oxygenated blood from the lungs. In terms of function, the unoxygenated blood from the right ventricle is pumped out by way of the aorta to the systemic circulation and is returned to the right atrium by way of the venae cavae. The oxygenated blood is returned by the pulmonary veins to the left atrium and then is pumped out to the lungs again via the pulmonary artery (see Fig. 1, *Defect*). Thus, because the great arteries are transposed without a corresponding alteration in the great veins, the systemic and pulmonary circulations are basically separate. However, some mixing of these bloods occurs through various compensating anomalies which send some oxygenated blood through the systemic circulation and permit variable periods of tenuous survival.

Grossly, the great vessels, in contradistinction to their normal relationship, always appear with the aorta anterior and the pulmonary artery posterior. Anatomically, transposition may be definitely recognized whenever there is an anterior shift of the aorta and a posterior shift of the pulmonary artery in relation to the ventricles (Fig. 2). This fact also serves to distinguish transposition from dextrocardia, or inversion, where the shift is from left to right (mirror image of the normal) rather than anterior and posterior.

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*Also known as complete uncorrected transposition of the great vessels, transpositio vera, or crossed transposition.

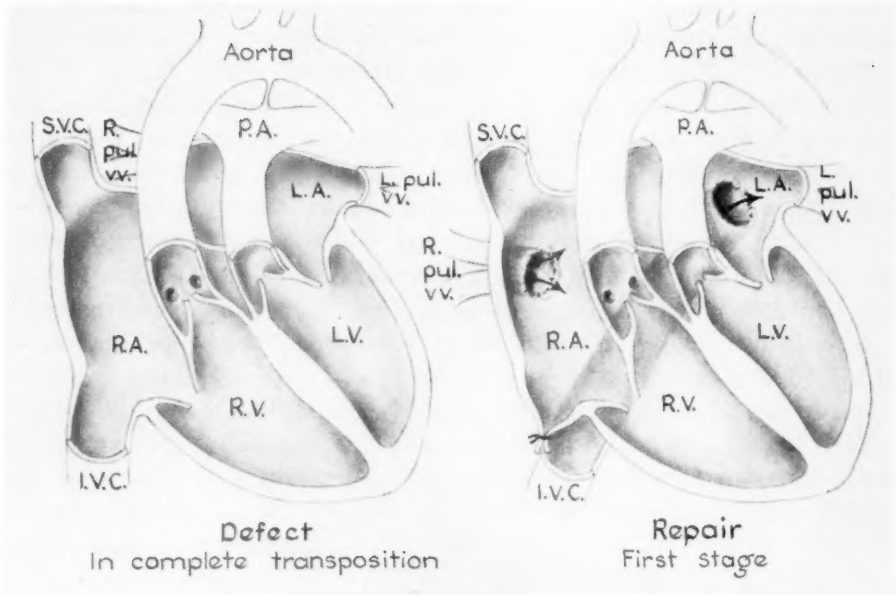

Fig. 1.—*Defect* in complete transposition of the aorta and pulmonary artery, and *repair* (first stage) by anastomosing right pulmonary veins to right atrium and the inferior vena cava to the left atrium.

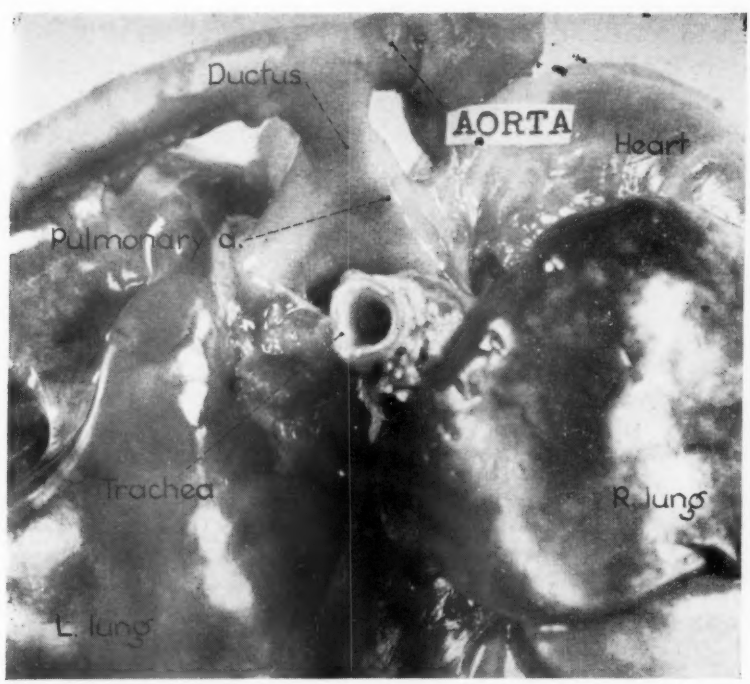

Fig. 2 (Case 4, Table III).—Complete transposition of the great vessels with patent ductus arteriosus surviving four weeks (viewed from above and behind). Note anterior position of aorta in relationship to the pulmonary artery.

Partial Transposition.—This condition exists when both the aorta and the pulmonary artery arise from the same ventricle (either the right or the left), or from a common ventricle in a transposed relationship.

"Corrected" Transposition.—In this condition, the aorta and pulmonary artery are transposed as in complete transposition. On gross inspection one notes the anterior position of the aorta and the posterior position of the pulmonary artery; however, there is no physiologic abnormality, because in spite of this transposition, or shift in position of the great vessels, the pulmonary artery arises from the ventricle receiving systemic venous blood, and the aorta arises from the ventricle receiving the oxygenated pulmonary venous blood.

It should be mentioned that it is preferable to drop the terms right and left ventricle in defining complete and "corrected" transposition, and to substitute definitions in terms of function such as "systemic venous ventricle" or "pulmonary arterial ventricle," because in a given case of complete transposition the systemic venous ventricle giving rise to the aorta may structurally resemble either the left ventricle (bicuspid valve, etc.) or the right ventricle (tricuspid valve, etc.)

INCIDENCE AND PROGNOSIS

At autopsy in patients with congenital heart disease, complete transposition, formerly thought to be a rare lesion, is a commonly found form of congenital cyanotic heart disease. Its total incidence may even exceed that of tetralogy of Fallot.

In view of the fact that the rarity of this lesion has often been stressed, it is of interest to review in Table I some of the autopsy series in which the incidence of complete transposition has approached or actually exceeded in frequency the finding of the much better known tetralogy of Fallot. Moreover, in almost all of these series, if one considers only deaths occurring in infants, the incidence of complete transposition far exceeds tetralogy as the chief cause of death in this age group.

TABLE I. COMPARATIVE FREQUENCY OF COMPLETE TRANSPOSITION AND TETRALOGY OF FALLOT (AUTOPSY DATA)

AUTHOR AND (SOURCE OF CASES)	PERIOD COVERED	TOTAL NO. OF CASES OF CONGENITAL HEART DISEASE	INCIDENCE	
			COMPLETE TRANSPOSITION (PER CENT)	TETRALOGY OF FALLOT (PULMONIC STENOSIS WITH INTERVENTRICULAR SEPTAL DEFECTS) (PER CENT)
Abbott[4] (collected)	-to 1931	1,000	5	8
Leech[5] (Johns Hopkins)	1889-1933	75	9.3	5.3
Gibson[6] (Childrens Memorial, Chicago)	1921-1936	105	8.5	7.6
Rannels et al[7] (Hospital of University of Pennsylvania)	1874-1936	36	13.9	9.3
Keith[8] (city of Toronto registry)	1948	29	13.8	17

Also, in regard to incidence, both Abbott[9] and Brown[10] have commented upon the fact that, even though the heart in complete transposition is a striking object with the aorta arising anteriorly from the right ventricle, the condition may be easily, and is frequently, overlooked. Contributing factors to this latter occurrence are the small size of the heart, since death usually occurs in infancy, and the fact that at least 50 per cent of the patients have intact ventricular and atrial septa which may give the heart a superficial appearance of normality. In reviewing our own autopsied series of twenty-six cases of complete transposition and one partial transposition found in the years between 1946 and 1952, we have noted several such occurrences of missed diagnoses which were later detected by a more systematic observation of the autopsy material. Further analysis of our own autopsy material provides additional circumstantial evidence on the apparent frequency with which this condition may be overlooked. In the three years from 1946 to 1948 inclusive, complete transposition was apparently diagnosed only twice at autopsy in our hospital, whereas in the next three years from 1949 to 1951 inclusive, it was found in thirteen patients. This striking increase was not due to any interest in surgical treatment since the latter was not instituted until 1952, but rather reflects the active interest of our pediatric diagnosticians in attempting to make a definitive diagnosis in every case of congenital heart disease, particularly if the patient is not doing well. As a result, in our own clinic during the past two years, the number of new patients diagnosed as having complete transposition has slightly exceeded the number of new patients with tetralogy of Fallot. Moreover, it is this fine diagnostic accomplishment by our pediatric cardiologists that has stimulated our efforts to do something about correcting this lesion.

The bleak prognosis associated with complete transposition is indicated for a representative series of cases in Table II. It may be noted from these data that, although three-fourths of the infants survived at least four weeks, less than one-fourth are alive at the end of the first year. Since complete transposition places no increased burden upon the fetal circulation, these children are nearly always born in good condition. In fact, stillbirth occurring in association with transposition is usually due to some other cause. In our own series of twenty-nine cases of complete transposition, there was only one stillbirth (due to an associated erythroblastosis); five other patients died during the first month. No patient died during the first week of life, two died in the second week of life, one in the third week, and two during the fourth neonatal week.

TABLE II. CYANOTIC HEART DISEASE: COMPARISON OF SURVIVAL OF UNTREATED PATIENTS

MOST FREQUENT TYPES	PER CENT ALIVE AT			
	BIRTH	1 MO.	1 YR.	7 YR.
Complete transposition (114 cases*)	95	72	22	4
Tetralogy of Fallot (Campbell-Guy's Hospital clinic[12])				50

*Eighty-five cases collected by Kato[11] plus twenty-nine from University of Minnesota.

Thus, from a practical viewpoint, sufficient time exists in most instances for this lesion to be diagnosed and therapy instituted. Moreover, it is obvious

from inspection of Table II that, unlike tetralogy of Fallot where approximately one-half of the children live to the age of 7 years, in complete transposition the backlog of undiagnosed cases from other years is almost nonexistent. In fact, Hanlon and Blalock[1] in a series of 123 collected cases of complete transposition found that the average survival time was only nineteen months and, when the six patients surviving more than ten years were subtracted from this series, the average duration of life for the remaining 117 was only five and one-half months.

DIAGNOSIS

The diagnosis in the typical case of complete transposition is usually not difficult, provided there is an awareness by the examiner of the relatively frequent existence of this condition in infancy.

The occurrence of the characteristic triad of persistent and severe cyanosis, dyspnea, and failure to gain weight in an infant suggests the possibility of the presence of complete transposition of the great vessels. The cyanosis nearly always is first noticed shortly after birth, and becomes progressively more severe in a matter of days or weeks. The dyspnea is obvious and frequently persists even in an atmosphere of oxygen.

Taussig[13] has discussed the roentgenographic findings in cases with complete transposition of the great vessels. Briefly, the shadow at the base of the heart resulting from the great vessels is often narrow, because the aorta lies directly in front of the pulmonary artery. In the oblique projection, the roentgenographic shadow caused by these great vessels is widened beyond normal; in the anteroposterior view, the heart is usually much enlarged and the pulmonary vascular markings are often exaggerated, which are points of considerable value in distinguishing these lesions from tetralogy of Fallot. However, it should be emphasized that, at birth, the heart in complete transposition is usually of normal size and, while the subsequent enlargement usually takes place rapidly, there may be considerable variation, so that a small heart in a cyanotic infant does not preclude the diagnosis of complete transposition.

Murmurs, usually systolic, are present in most cases, but may be absent and seem to be of little value in the diagnosis.

Cardiac catheterization has not been particularly helpful in this series in the diagnosis of complete transposition unless a high degree of suspicion as to its presence already existed. However, the physiologic data acquired concerning pressures, saturations, and shunts may be helpful. Extreme desaturation of the venous blood in the venae cavae or right atrium, as well as of the arterial blood in the aorta (Case 16, Table III), is characteristic in these patients and constitutes adequate physiologic explanation for their severe incapacitation and short life.

Angiocardiography, by injection of opaque media into a systemic peripheral vein, is very helpful in establishing the diagnoses of complete transposition. Angiograms were performed in nine of our patients with no serious complications. The findings of successive opacification of the vena cava,

right auricle, right ventricle, and the aorta arising from the latter in an anterior position before any shadow is seen in the pulmonary artery are diagnostic of complete transposition. Also, frequently the presence of shunts may be detected or suspected from this examination.

ASSOCIATED ABNORMALITIES

It has been well recognized that complete transposition is usually incompatible with a prolonged existence unless an associated defect is present to allow some mixing of blood between the two basically separate pulmonic and systemic circulations. We have analyzed in Table III the relationship between the duration of life and the presence of associated shunts or septal defects for the twenty-nine patients with complete transposition seen at this clinic. We have been impressed by the fact that remarkably minimal-type shunts may serve to keep these infants alive for sufficient time to make the diagnosis and to institute corrective treatment. This observation has some practical importance to the surgeon with a view to the performance of corrective procedures. Thus, in nine or approximately one-third of our twenty-nine patients with complete transposition the associated defect consisted only of a patent foramen ovale or a patent foramen ovale together with a patent ductus. The average duration of life of these nine infants was three and one-half months and, if the three patients are added with interatrial defects, which is becoming a correctable lesion, the percentage of children with potentially curable-type associated anomalies approaches one-half of the entire group. Obviously this finding would assume greater importance the moment that we are able to correct satisfactorily the transposition present.

The remaining fourteen patients in our series had interventricular defects alone or combined. Hanlon[1] has surveyed the literature and summarized the relationship between the duration of life and the type of shunt or shunts. He found that a large interventricular defect offered the best compensating abnormality for survival. In fact the longest reported[14] survival of a patient with complete transposition occurred in a woman living until the age of 56 years, who had a single ventricle (cor biatriatum triloculare). It may be anticipated that any patient with a sizable ventricular defect is likely sooner or later to acquire pulmonary hypertension.

An interatrial septal defect was the next most favorable isolated defect, and the combination of an interatrial with an interventricular septal defect gave the best prognosis of all. These findings constitute the basis for their[2] preferred method of treatment of complete transposition by production of an interatrial defect.

These septal shunts existing in complete transposition differ considerably from similar shunts in hearts without transposition. Because in complete transposition all of the blood pumped out of the heart is returned to the same side of the heart, and because the two circulations are therefore basically separate, any shunts occurring between the systemic and pulmonary circuit must take place in both directions in a balanced manner lest one side be bled "dry" while the opposite became plethoric. As Blalock[2] has emphasized, this necessity of

TABLE III. COMPLETE TRANSPOSITION*: DURATION OF LIFE CORRELATED WITH PATHOLOGY

PATIENT	SEX	AGE AT DEATH	ASSOCIATED ABNORMALITIES					DATE FIRST SEEN (MO. AND YR.)	SURGICAL TREATMENT
			PATENT FORAMEN OVALE	PATENT DUCTUS ARTERIOSUS	INTERATRIAL DEFECT (SIZE IN MM.)	INTERVENTRICULAR DEFECT (SIZE IN MM.)	OTHER		
1. E. J.	M	7½ mo.	√					7/51	
2. S. S.	M	2 mo.	√					6/48	
3. L. M.	M	22 da.	√	√				11/52	
4. K. O.	F	1 mo.	√	√				12/52	Died preoperatively
5. G. B.	F	Stillborn	√	√			Erythroblastosis	10/52	
6. D. S.	M	9 da.	√	√				4/50	
7. P. G.	F	2 wk.	√	√				8/51	
8. C. D.	F	7 wk.	√	√				8/52	Died preoperatively
9. J. N.	M	4 mo.	√	√				8/51	
10. B. P.	F	17 mo.			10			11/51	Transposition great veins†
11. J. L.	M	2 yr.			10			3/51	Transposition great veins†
12. K. D.	F	7 wk.			10		Hypoplastic right ventricle	12/52	Transposition great veins†
13. G. G.	F	17 mo.				10, 20 (2 defects)		1/51	Transposition pulmonary veins‡
14. R. R.	M	4½ yr., living				By catheterization		1/49	Transposition pulmonary veins‡

TABLE III—CONT'D

PATIENT		SEX	AGE AT DEATH	ASSOCIATED ABNORMALITIES					DATE FIRST SEEN (MO. AND YR.)	SURGICAL TREATMENT
				PATENT FORAMEN OVALE	PATENT DUCTUS ARTERIOSUS	INTERATRIAL DEFECT (SIZE IN MM.)	INTERVENTRICULAR DEFECT (SIZE IN MM.)	OTHER		
15.	B. H.	F	8 wk.	√			High (22 x 4)		4/50	
16.	D. G.	M	7 mo.	√			5, 3 (2 defects)	Preoperative O_2 saturation rates ventricle 19%, femoral artery 22%	5/52	Transposition pulmonary veins‡
17.	L. E.	M	13 mo.	√			High (10)		8/50	
18.	G. D.	M	2 mo.	√			High (8)		8/51	
19.	C. T.	M	11 wk.	√	√		High (4)		12/52	Transposition great veins†
20.	N. K.	F	5 mo.	√	√		High (15)	Coarctation aorta	8/49	
21.	R. S.	M	24 da.	√	√		High (2)		9/46	
22.	G. B.	M	5 mo.			5	High (5)		12/51	
23.	J. G.	M	13 mo.			15	Complete	Cor biatriatum triloculare	6/50	
24.	B. H.	F	8 mo.			4	High (20 x 10)	Valvular pulmonary stenosis	6/52	Died preoperatively
25.	B. G.	F	18 mo.			3 x 4	High (13 x 10)	Bing-Taussig transposition	6/52	Transposition great veins§
26.	W. V.	M	3 mo.		√	5	High (10)	Complete coarctation aorta	8/52	
27.	J. M.	F	3 wk.		√	√	√	Coarctation‖	10/52	
28.	G. W.	M	6½ yr., living				√		9/51	
29.	C. B.	M	4½ yr., living				By catheterization		10/49	

*University of Minnesota Series 1946 to 1952.
†Anastomosis of right pulmonary veins to right atrium and inferior vena cava to left atrium in one stage.
‡Anastomosis of right pulmonary veins to right atrium.
§Anastomosis of right pulmonary veins to right atrium and superior vena cava to left atrium in two stages.
‖Complete interruption of aorta at its isthmus, distal aorta arising from patent ductus.

maintaining the circulations balanced is a matter of practical importance to the surgeon contemplating some form of extracardiac shunt as a treatment. As shall be discussed later, failure to achieve this balance adequately is the apparent cause of most of the failures of surgical treatment occurring in this series. Moreover, it is quite likely that the usual mechanism of death in these infants is the result of an acute upset in this precarious balance.

SURGICAL MANAGEMENT OF TRANSPOSITION

General Considerations.—Blalock[1-3] has very thoroughly discussed the several possibilities for surgical treatment existing in this malformation. It would be foolish to challenge the concept that our therapeutic goal in surgery for transposition of the great arteries should be the complete anatomic correction of that anomaly. This achievement would restore an aorta to the left ventricle and a pulmonary artery to the right ventricle. However, desirable as this restitution would surely be, its accomplishment is difficult to conceive. A well-nigh insurmountable problem is created by the coronary vessels' origin behind the aortic valvular cusps and at the very root of this great vessel. Restitution of the great arteries to the proper ventricles with the anastomosis made distal to the coronary arteries would leave both coronary arteries still receiving only venous blood from the right ventricle, which is in itself an even more severe malformation (anomalous origin of both coronary arteries) than complete transposition.

In view of the substantial obstacles just cited, the arterial repositioning idea was temporarily abandoned by us. Another possibility, and what might be thought of as a reciprocal of the first method, was considered. This alternative approach examined the technical possibility of transposing the systemic and pulmonary veins in such a way as to compensate for the transposed arterial trunks. Blalock,[3] in considering this possible method for the management of transposition, was attracted by its possibilities, although he apparently thought it technically unfeasible to consider completely transposing both of the venae cavae and all of the pulmonary veins.

The successful complete transposition of all of these great veins in a patient with complete transposition would result in the circulation of a corrected transposition. Essentially then, the right ventricle would continue as the systemic pumper and would continue to be filled via the right auricle which now, however, would receive all of the arterialized pulmonary venous return. The left ventricle would continue to maintain the pulmonary circuit after accepting systemic venous blood from the cavae now directed into the left auricle. The initial stage of such a realignment of the veins is portrayed diagrammatically in Fig. 1.

If the technical problems that may be involved are ignored temporarily, it will be readily apparent that this plan of operative management for patients with anomalous arterial alignment offers several very attractive advantages. First, the coronary vessels would be provided with oxygenated blood. Second, a virtually curative operation could be provided in certain instances, namely,

the substantial group of patients without septal defects. And finally, the characteristically severe cyanosis would disappear in almost all patients as soon as both venae cavae were successfully moved to the left atrium.

Somewhat paradoxically, the graver the child's condition before surgery, the greater the likelihood of completely curative surgery being technically possible. In other words, palliation is provided to these children by hemodynamically large interatrial and/or interventricular septal defects. And, on the contrary, many of the more sorely crippled infants eke out an existence with only a functionally patent foramen ovale or a patent ductus as the sole intracardiac shunt. In such patients as the latter, the successful repositioning of the systemic and pulmonary venous returns should thereby prove quite beneficial and even compatible with a normal life. Recognition of the correlation between poor physical condition and fewer internal shunts has caused us to adopt the procedure of operating upon these desperately ill infants as an emergency procedure as soon as the diagnosis is established unless compelling contraindications, which can be improved by further delay, exist. Prior to adopting this policy, three infants tentatively scheduled for surgery the next day died preoperatively between the time the diagnosis was made and the nominal delay coincident with scheduling.

For those patients with the associated septal defects, by transposing the systemic and pulmonary venous returns there is a strong prospect for improving the oxygen content of the blood in the systemic circuit. This operation might prolong life and thereby significantly lower the appalling death rate cited earlier in the text as associated with this condition. For those so salvaged, hope could then arise for the likelihood of corrective intracardiac surgery at some future date.

Assuming that complete transposition of the veins can be successfully carried out, it is interesting to speculate upon the prognosis that might be anticipated.

Most available evidence would seem to indicate that life expectancy should be nearly normal. Since the right ventricle would continue to be the systemic pumper, the question might be raised as to whether there are any important inherent differences known to exist between the ventricles. Numerous physiologic and clinical observations would seem to indicate that the differential development of the ventricles after birth is conditioned almost entirely by mechanical factors, and that ample adaptive power exists for one ventricle to perform the functions normally carried out by the other.

Another very practical point in this regard, and we have alluded to it in the discussion under terminology, is the fact that in several varieties of complete transposition the ventricle occupying the position of the normal right ventricle, and therefore discharging systemic venous blood into the aorta, is structurally and embryologically not the right ventricle at all but represents instead a transposed left ventricle.

Since we are proposing to treat complete transposition by creating in effect a form of corrected transposition, it is also of interest to examine the recorded prognosis of this latter anomaly.

Interestingly enough, corrected transposition without septal or other defects appears to be one of the rarest of reported congenital cardiac anomalies. Embryologically this would not be expected, in fact quite the contrary might be anticipated; thus the conclusion seems inescapable that many patients so afflicted live a normal life expectancy, and the abnormal anterior position of the aorta is not detected even at autopsy unless they happen to have some other associated septal defects. Walmsley,[15] in 1931, reported a unique case of corrected transposition without associated anatomic defects. The man lived an active life, dying however at 35 years of age, apparently as the result of a complete heart block* which had been present for at least ten years preceding.

A second case, even more unusual, was reported by Graanboom[16] in 1891. It is of the utmost interest in this regard because it appears to be the only such case recorded, and because it shows similarity to our proposed surgical correction. This patient had a complete transposition combined with an additional defect consisting of situs inversus of only the atria and no other septal or associated defects. As a result, both venae cavae returned the systemic venous blood to the left atrium from which site it entered the ventricle supplying the pulmonary artery. All of the pulmonary veins entered the right atrium and from there entered the ventricle from which the aorta originated. Thus, the circulation in this patient appears to be identical with our proposed operative correction for complete transposition. This patient was described as a previously active and robust man, who died at the age of 33 years from the complications of chronic diffuse nephritis. He had no apparent cardiac abnormalities until the final illness.

Results.—To date, eight patients with complete transposition have had nine operative procedures performed. Their ages range from 7 weeks to 3½ years. All the patients have had the diagnosis of complete transposition confirmed at surgery or by autopsy.

Four types of surgical operations are described here. Three of these have been performed one or more times in this series of patients, and the fourth has been proposed to overcome some of the difficulties believed to be associated with acutely unbalancing the circulations.

Types of Venous Anastomoses.—

1. Anastomosis of the right superior and inferior pulmonary veins to the right atrium: This anastomosis is illustrated in Fig. 3 (*a*, *b*, and *c*) and in Fig. 5.

2. Anastomosis of the right superior and inferior pulmonary veins to the right atrium together with the inferior vena cava to the left atrium: The general plan of this anastomosis is portrayed graphically in Fig. 1, steps in its technical accomplishment are shown in Fig. 3, and it is photographically illustrated in Figs. 5 and 8.

3. Anastomosis of the left innominate (cardiac end) vein to the left auricle with ligature of the superior vena cava: This type of anastomosis is depicted in Fig. 10, *a*.

*This was thought to be explicable possibly upon the abnormal deviation of the interventricular septum that occurs in corrected transposition.

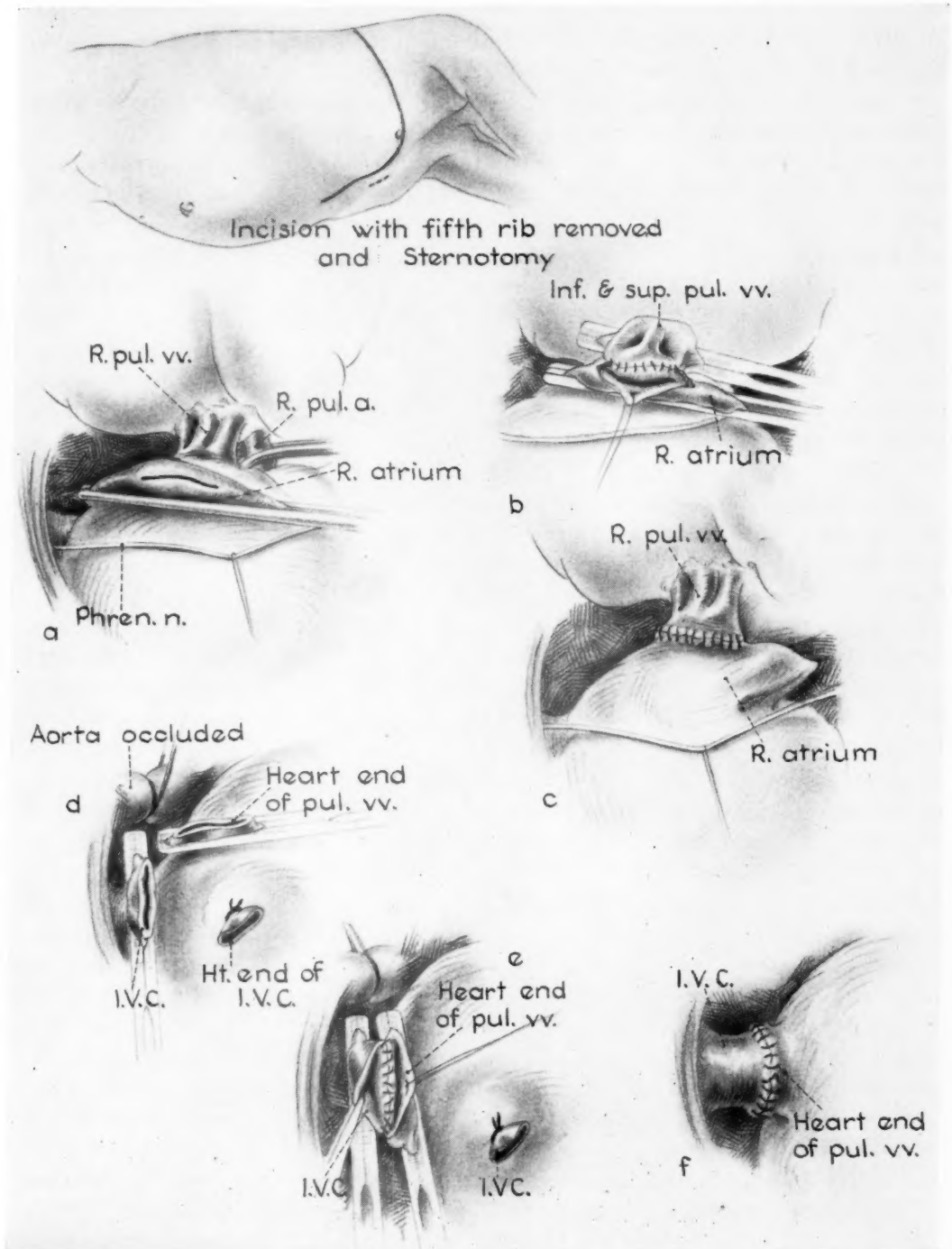

Fig. 3.—Incision and operative techniques for great vein anastomoses. *a*, *b*, and *c*, Anastomosis of the right pulmonary veins to the right atrium. *d*, *e*, and *f*, Anastomosis of the inferior vena cava to cardiac end of the transected right pulmonary veins.

4. Anastomosis of the superior vena cava to the left atrium with a temporary polythene shunt maintained between the superior vena cava and right atrium: This is a proposed operation (illustrated in Fig. 10, *b*) which we believe will be less likely to precipitate circulatory unbalance.

Operative Techniques.—Several positions and incisions have been tried, depending on the anastomosis to be carried out in a specific case.

For the transposing of the right pulmonary veins to the right atrium, and the inferior vena cava to the left atrium, the best exposure has been obtained with the patient in a lateral (slightly anterior) position as indicated in Fig. 3. The incision is made through the bed of the right resected fifth or sixth rib and cartilage to the midsternum, and thereafter vertically down the latter to below the xiphoid as a sternotomy. It has not been necessary to open the diaphragm. With this exposure, access is excellent to all the hilar structures of the right lung, both cavae, and particularly the thoracic component of the inferior cava and adjacent aorta, as is indicated photographically in an infant with transposition (Fig. 4).

For transposing of the superior vena cava, an anterior transverse sternotomy extending bilaterally into the third or fourth interspace as illustrated in Fig. 10, *c* provides handy access to the right atrium, superior vena cava, and innominate veins, and a fair exposure to the posteriorly placed, and often small, left auricle.

With either incision, and the chest wall open, the pericardium is incised widely to define and confirm by inspection and by palpation the type and variety of anomaly present, that is, a high pressure within the pulmonary artery, for instance, is strongly suggestive of an associated high interventricular defect. The anterior position of the aorta arising from the right ventricle and the posterior position of a pulmonary artery springing from the left ventricle confirm the preoperative diagnosis and, save in the rare case of corrected transposition, could hardly be confused with any other cardiac lesion.

Anastomosis of the Right Pulmonary Veins to the Right Atrium.—At the initial stage, we have usually proceeded to anastomose the right superior and inferior pulmonary veins to the right atrium after divesting it and the adjacent pulmonary artery of surrounding alveolar tissue and pericardial attachments. The successive technical steps in accomplishing this anastomosis are illustrated in Fig. 3 (*a, b,* and *c*). Our technique seeks to minimize pulmonary blood flow during this anastomosis with an occluding ligature or appropriate clamp on the right pulmonary artery during the interval of occlusion of the corresponding right pulmonary veins. Despite this precaution, a certain degree of pulmonary edema usually develops if the venous exit from the lung remains closed for more than about fifteen minutes, probably because of congestion provoked by the bronchial collateral arterial inflow during this interval. The anesthetist usually is the first to identify the onset of this complication by the appearance of an increasingly troublesome volume of bloody serous fluid in the endobronchial aspirations. This pulmonary edema has apopened and the pulmonary venous pressure thereby lowered. We have customarily sutured, with a single coapting row of 000000 silk, the right pulmonary

veins to an equal-sized opening in the side of the adjacent right atrium utilizing a Potts-type clamp to occlude a knuckle of the latter (Fig. 5). To obtain a single ostium from the multiple tributaries draining the right lung, a portion of the left auricular wall is included on the pulmonary side of the divided vein. Suturing to the atrial wall is simplified by this maneuver. Examination of this anastomosis in one long-term (five months) and several

Fig. 4.—Operative exposure to pulmonary hilar structures in patient with complete transposition (photograph). Note the favorable anatomic relationships which allow the realignment of the great veins entering the heart.

short-period survivors has demonstrated a widely patulous, thoroughly ample new opening in all cases (Fig. 6). At the conclusion of this shunt, brightly oxygenated blood may leak momentarily from the suture line or even, at times, be visible through the semitranslucent auricular wall as a pinker swirl amid the duskiness of the unsaturated caval return.

In our first four patients operated upon for complete transposition, the operation was terminated at this stage with two successes. The defect in the left auricle (cardiac end of the right pulmonary vein) was closed in these same four cases by either running or interrupted silk sutures. In the next four patients, the cardiac end of the transected pulmonary veins provided the stoma to which the transected inferior vena cava was united to the left atrium as illustrated in Fig. 8.

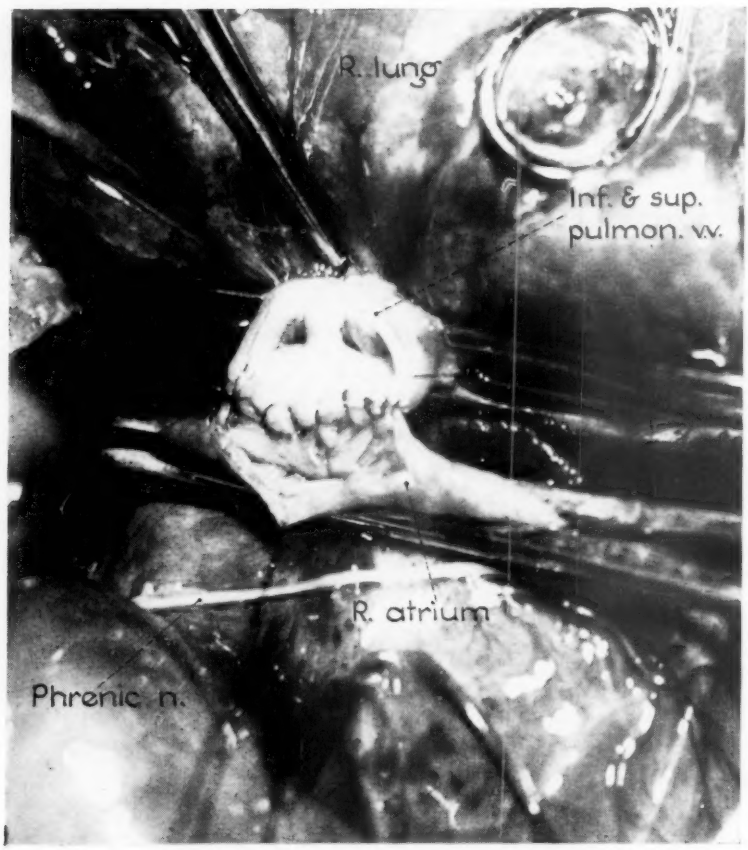

Fig. 5.—Anastomosis of right pulmonary veins to right atrium for complete transposition (photograph). Note: Posterior row of anastomosis completed; the pulmonary veins are transected with an attached cuff of left atrial wall.

As was mentioned, four patients with complete transposition had the right pulmonary venous return completely diverted into the right atrium as the sole operative procedure. There were two successes and two failures in these four patients. These results are summarized in Table IV, and some of the pertinent observations will be briefly considered as follows:

R. R. (Case 14, Table III) had rather a typical history for a patient with complete transposition and a fairly large interventricular defect. He had been cyanotic since birth; growth and development had been slowed. He had been seen preoperatively a number of times in our clinic because of severe dyspnea and the almost continuous occurrence of respiratory infections. Before surgery, he was deeply cyanotic with a superior vena caval and right atrial oxygen saturation of only 10 per cent. The femoral artery oxygen saturation was

37 per cent, hemoglobin was 19 Gm. with a red blood cell count of 8.25 million. The heart was typically enlarged and, although the patient was 3½ years of age, he did not walk except for an occasional one or two steps.

Operation was performed on March 21, 1952. The findings were typical for complete transposition with pulmonary hypertension confirming the diagnosis of an interventricular defect. The right pulmonary veins were anastomosed to the right atrium. During the time of cross-clamping of the pulmonary veins for this anastomosis, seventeen minutes elapsed, and a rather severe pulmonary edema occurred in the entire right lung despite the fact that the right pulmonary artery had been likewise occluded.

He convalesced uneventfully, and his improvement has been described by all observers as remarkable. He now is walking. There has been only one episode of respiratory infection since surgery. Although still cyanotic, his color is much improved and the femoral artery oxygen saturation on Nov. 6, 1952, approximately eight months after surgery, was 61 per cent. Hemoglobin is now 16.8 Gm. A second stage procedure, designed to transpose one or both venae cavae, is planned for this patient.

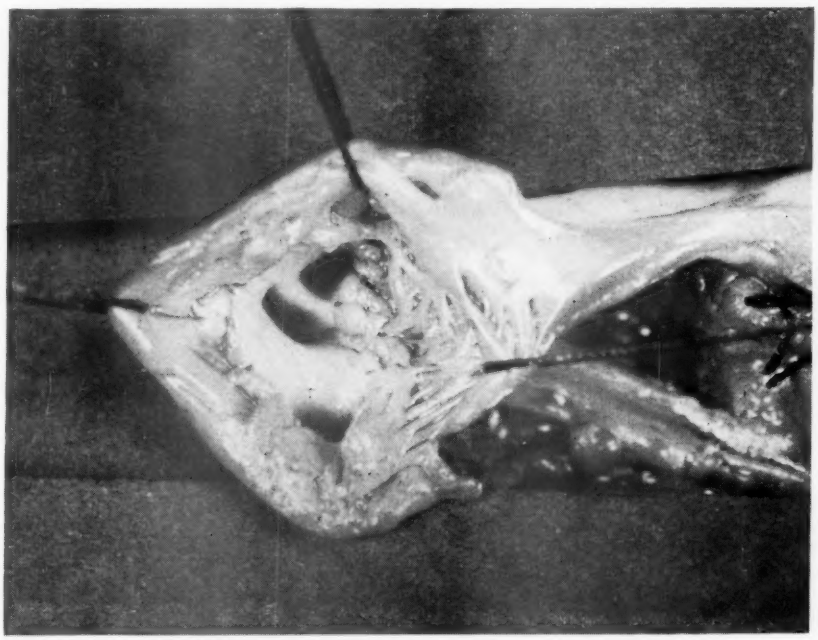

Fig. 6 (Case C. T., Table V).—Completed right atrial right pulmonary venous anastomoses viewed from within right atrium of an operative specimen. Patulous lumen obtained in 11-week-old infant.

B. G. (Case 25, Table III), who was 18 months of age at the time of the first operation performed June 20, 1952, was the second success and the third patient operated upon. Prior to operation, this infant was severely cyanotic with an arterial saturation of only 32 per cent. She was troubled with frequent respiratory infections, and was unable to sit up, although she was 18 months of age. The heart was enlarged on roentgenogram (Fig. 7, *a*) and had the typical findings suggestive of transposition.

On June 20, 1952, the right pulmonary veins were anastomosed to the right atrium without incident. Following surgery the patient showed a gradual and continued improvement. The most striking changes were an improvement in the cyanosis and a gain in appetite, which prior to surgery had been extremely poor. The reduction in heart size that occurred four months after this surgical procedure was gratifying (Fig. 7, *a* and *b*).

Unfortunately, this nice result was beclouded by the tragedy of subsequent events. She was readmitted for performance of a second stage procedure to move the superior vena caval

blood into the left atrium. On Nov. 14, 1952, through an anterior sternotomy incision as indicated in Fig. 10, *c*, an anastomosis of the cardiac end of the left innominate vein to the left atrium was carried out without incident as illustrated in Fig. 10, *a*. The superior vena cava was ligated at the heart entrance, thus making the shunt obligatory.

Two hours later, progressive distention of the head and neck veins had become apparent. The chest was reopened, and the left innominate vein-left atrial anastomosis was resected and reperformed. Just at the conclusion of this second anastomosis, the heart ceased and resuscitation was unsuccessful.

At autopsy, the right pulmonary to the right atrial anastomosis, performed approximately four months earlier, was widely patent. The second innominate vein to the left atrial anastomosis was also patulous. The transposition was of the Bing-Taussig type with a small interatrial defect and a fairly large high interventricular defect.

Inspection of the resected unsuccessful innominate vein to the left atrial anastomosis indicated that the technical error was in utilizing the very tip of the left auricle for the site of this anastomosis. Since the vessel lengths were entirely ample, this need not have been necessary. Failure was due to the numerous fine trabeculae which stretched across the lumen and acted as a nidus for a few tiny blood clots which were sufficient to obstruct this low pressure area.

TABLE IV. COMPLETE TRANSPOSITION: RESULTS OF ANASTOMOSIS OF RIGHT PULMONARY VEINS TO RIGHT ATRIUM

PATIENT	AGE	RESULT	OTHER DEFECTS
1. R. R.	3½ yr.	Excellent improvement, femoral artery O_2 saturation increased from 37% preoperative to 61% 8 mo. after operation	Probably interventricular defect
2. G. G.	17 mo.	Died, 24 hr. postoperatively, heart failure	Two interventricular defects, 10 and 20 mm.
3. B. G.	18 mo.	Improved,* heart decreased in size	Pulmonary-atrial anastomosis patent and well healed, interatrial defect 4 mm., interventricular defect 13 × 10 mm.
4. D. G.	7 mo.	Died, 48 hr. postoperatively, heart failure	Two interventricular defects, 5 and 3 mm., patent foramen ovale

*Died 5 mo. later at second-stage operation.

We soon appreciated the need for balancing, with a part of the caval blood flow, the decreased venous return to the left side, once the return from one lung had been shunted to the right auricle. It is assuredly not alway compulsory to make this adjustment, for the patients described in the successful cases survived and improved without a compensatory second shunt. However, two others (Cases 2 and 4, Table IV) probably died once the pulmonary venous right atrial anastomosis was working because of the absence of an adequate mechanism (collateral septal defects) for prompt establishment of a reasonable volume equilibrium between the two circuits in the face of a substantial increased return to the right atrium with each heartbeat.

Anastomosis of the Right Pulmonary Veins to the Right Atrium, and the Inferior Vena Cava to the Left Atrium.—Upon the basis of the observations recorded in respect to duration of survival and type and number of associated abnormalities, summarized in Table III, it has been contended by us that the fewer the associated anomalies in a child with transposition, invariably the poorer is the general condition, the greater the number of anastomoses required

to benefit him, and, hopefully, the better the ultimate chance for a definitive cure. Therefore, in an attempt to achieve a better approximate balance in venous return between the two circulations, we have tested in these next four patients, without success, the technical feasibility of anastomosing the systemic end of the divided inferior vena cava to the cardiac end of the divided right pulmonary veins after first completing the anastomoses of the right pulmonary veins to the right atrium. The resulting rerouting of the circulation following these shunts is illustrated in Fig. 1, and the successive technical steps in their performance are shown in Fig. 3 (*a* to *f*). The cardiac end of the inferior vena cava has been stick-tied and allowed to recede out of the way in these four patients. However, ultimately the possibility appears anatomically feasible for uniting the cardiac end of the divided inferior vena cava to the lung end of the

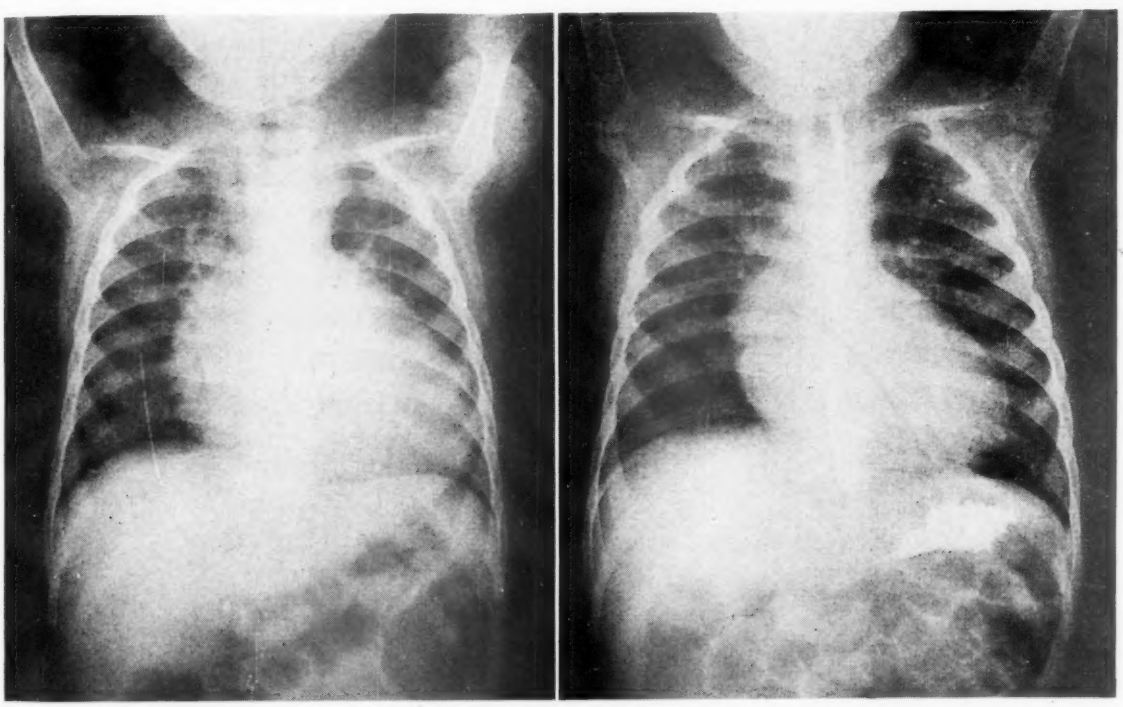

Fig. 7.—Decrease in cardiac size following successful right pulmonary-atrial anastomosis for complete transposition.

transected left pulmonary vein. To prevent abdominal visceral engorgement and shock-provoking stasis, the dorsal aorta was occluded above the diaphragm during the interval when the inferior vena cava was cross-clamped in making the anastomosis. The systemic end of the thoracic inferior vena cava was then anastomosed to the auricular end of the right pulmonary vein as is illustrated in Fig. 8, a photograph of a completed anastomosis. Once the inferior vena cava has been divided, the cardiac end of the pulmonary veins rotates into a satisfactory position for this union. The suturing position for this anastomosis was awkward and troublesome in the first two patients, and a fatal leakage occurred at this anastomosis in the first patient (Case 1, Table V) who might

otherwise have survived. We then came to extend the anterior end of the chest wall incision down the midline of the sternum to the diaphragmatic attachments, and the lengths of vessel which then became available for sewing, while not excessive, have been ample enough to allow a safe union by a single-layer running suture, coapting type, of 000000 silk. Fig. 9 illustrates the internal appearance of this inferior vena caval-left atrial anastomosis in one of the short-term survivors.

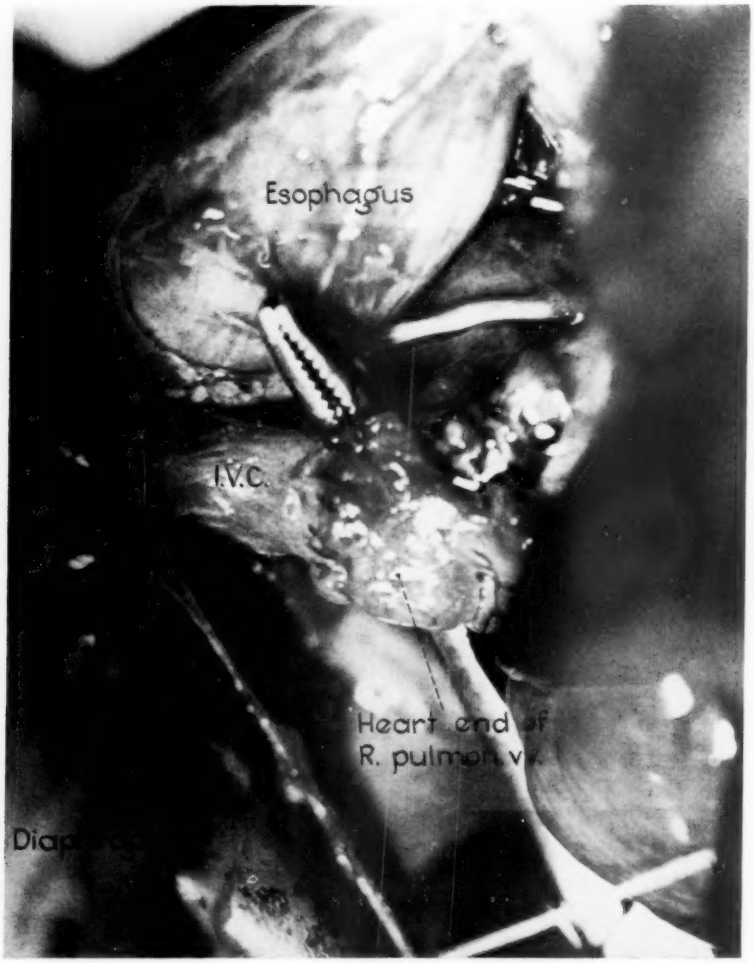

Fig. 8.—Completed anastomosis of inferior vena cava to left atrium (at the site of the cardiac end of the transected right pulmonary veins) (photograph).

One limiting factor, we believe, is the time required to complete this caval-left auricular anastomosis. During that interval, usually from fifteen to twenty minutes, the newly constructed pulmonary vein-right auricle anastomosis is open. This permits a considerable blood volume, and it can be an intolerable amount, to be pumped onto the right side of the circulation. In one child (Case 4, Table V), exactly this sequence of events was observed to happen. In this patient the right atrial circuit had insufficient abnormal chan-

TABLE V. COMPLETE TRANSPOSITION: RESULTS OF ANASTOMOSIS OF RIGHT PULMONARY VEINS TO RIGHT ATRIUM, AND INFERIOR VENA CAVA TO LEFT ATRIUM

PATIENT	AGE	RESULT	OTHER
1. B. P.	17 mo.	Died, 2 hr. postoperatively, hemorrhage from inferior vena cava anastomosis	Interatrial defect, 1 cm.
2. C. T.	11 wk.	Died, 8 hr. postoperatively, heart failure	Patent foramen ovale, interventricular defect 4 mm., patent ductus
3. K. D.	7 wk.	Died, 2 hr. postoperatively, heart failure	Rudimentary right ventricle, interatrial defect, 1 cm.
4. J. L.	24 mo.	Died, heart stopped 10 min. after pulmonary-atrial anastomosis completed. Restarted, and inferior vena cava to left atrial anastomosis rapidly completed, but heart ultimately failed again	Interatrial defect, 1 cm.

nels of adequate capacity to return it promptly to the left atrial side after the right pulmonary venous atrial shunt had been opened. Before our eyes, while preparing to perform the inferior vena cava anastomosis to the left atrium, we saw this patient's heart become pumped relatively dry on the left atrial side, and become distended on the right atrial side. Cardiac arrest occurred in less than ten minutes in this patient from the time of opening the right pulmonary venous-atrial anastomosis. Since the total blood volume in such an infant of a few kilograms weight is so small, shifts of only several hundred cubic centimeters can occur within a few hundred heartbeats and thus may prove rapidly fatal.

We now believe, therefore, that a previously prepared, but nonfunctioning, temporary and/or permanent preliminary shunt must be available so that once the blood flows from the pulmonary veins into the right auricle an appreciable amount of vena caval blood can be returned immediately to the left auricle in a compensating fashion. Minor volumetric imbalances can be remedied internally, it would seem, through existing mechanisms, once we can prevent the development of gross deficits and accumulations.

Our present plan, not yet tested but built on these chastening experiences, mostly failures, visualizes use of the azygos vein, cannulated with as wide a bore polythene tube as it will accept. With this polythene tube shunting the blood from the superior vena cava into the tip of the right auricle, the superior vena cava can be clamped and divided, and its systemic end can be anastomosed to the left auricle, without serious congestion of the upper body. The distal (cardiac) end is available for union with the right pulmonary veins. Until the pulmonary vein—right atrial suture line is completed, no blood need flow into the left auricle; therefore, both anastomoses can be opened simultaneously and the response to each can be somewhat monitored by the azygos-polythene shunt. The latter shunt will, of course, be discontinued prior to completion of the operation by ligation of the azygos vein and suture of the opening in the auricular appendage. The general plan for this proposed operation is illustrated in Fig. 10. In the absence of an adequately wide azygos,

the same general plan is applicable through the use of the left innominate vein. This latter structure we have employed for an anastomosis in one instance as illustrated in Fig. 10, *a*.

DISCUSSION

Although two patients out of the four in which the plan was attempted were substantially improved by a pulmonary venous—right atrial anastomosis, we believe that it is potentially hazardous to perform this anastomosis alone unless large internal shunts are known to exist.* In the absence of these latter, the rapidly lethal effects that occur due to unbalancing of the two basically independent circulations which exist in complete transpositions constitute sufficient reason for recommending only procedures designed to achieve hemodynamic equilibrium.

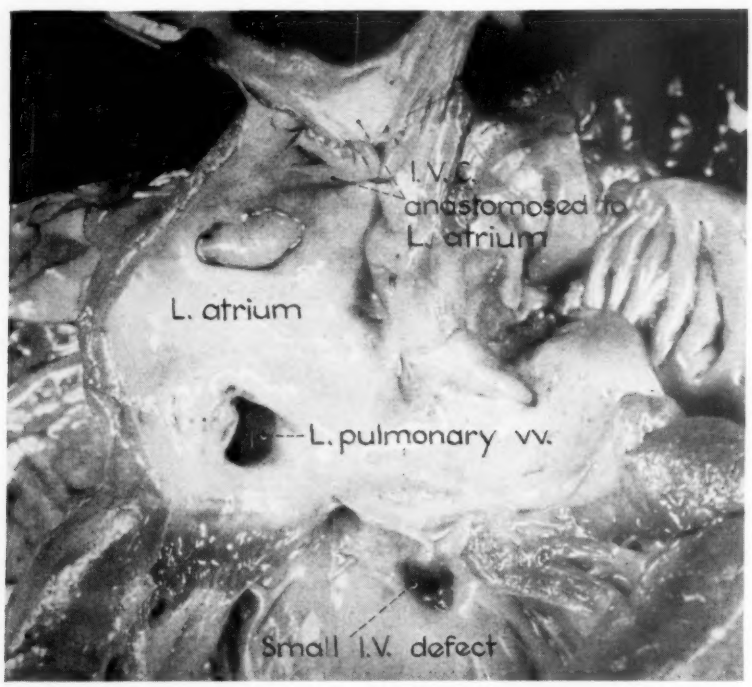

Fig. 9 (Case 19, Table III).—Anastomosis of inferior vena cava to left atrium (at site of transected right pulmonary veins) for complete transposition. Note: Photograph from within the left atrium of an operative specimen; also, a small interventricular defect may be seen.

Therefore, in the next series of four patients, the pulmonary-atrial anastomosis was performed first (with the thought of improving the systemic oxygenation), and then, at the same operation, the inferior vena cava was joined to the left atrium. Technical problems in obtaining adequate exposure to the inferior caval area occupied our attention in the first two patients in this series. They were then solved handily by the incision described (Fig. 3), and in the third case of this series both anastomoses were rapidly and smoothly carried out. However, this child had an additional unrecognized defect consisting of a rudimentary right ventricle which probably obviated hope for success. It was

*Since submission of this report, two additional patients with complete transposition and presumptive evidence of ventricular septal defects have had a right pulmonary venous to right atrial anastomosis only performed. These infants were aged 4 months and 19 months, respectively, and both have been substantially improved postoperatively.

not until the fourth and last case in this series that we realized that fatal unbalancing of the circulation could occur in the matter of the few minutes transpiring between the two anastomoses. This last case, then, has suggested the operation described previously (Fig. 10, *b*), whereby both the systemic and pulmonic shunts can be opened simultaneously. This latter maneuver appears practicable, and will be tested at the very next opportunity.

Some of these observations undoubtedly indicate the handicaps imposed by our inability to create in the experimental animal even a reasonably close counterpart of transposition as it is encountered clinically.

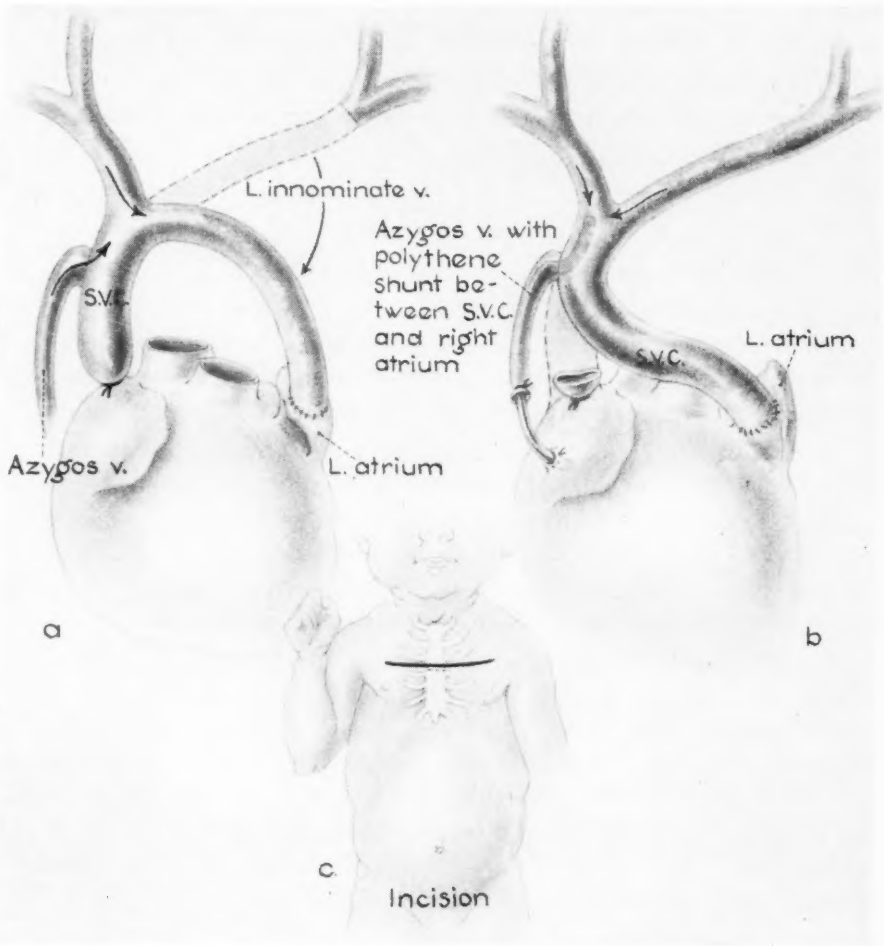

Fig. 10.—Operative techniques for transposing superior vena cava to left atrium for complete transposition of great arteries.

Thus, experimental testing of the several operative variants on the general plan of venous repositioning has been impossible. Therefore, questions as to just how many vessels and what vessels to reanastomose at one time have had to be worked out by the empiricism of trial and error. That method can be productive of a distressing series of disappointments, with the successes only partial, and thinly interspersed among the series.

Too gradually for one's peace of mind, our real knowledge of this problem's intricacies has been acquired. This technique of groping by trial-and-error testing of a number of variables yields answers painfully slowly since any one of many factors can bring about a failure, whereas a good result may even be fortuitous and may come about in spite of imperfections in the operative methods.

At present it is quite conceivable that the technical ability to perform these anastomoses has surpassed our physiologic and hemodynamic knowledge. However, in spite of these many failures, enough success has been obtained so far to make us feel that this general plan of venous repositioning is sound; and its successful prosecution will allow these otherwise doomed individuals real hope for long-term survivals and even cures.

An unanticipated dividend of the successful development of these techniques for venous anastomoses has been their application to cases with total anomalous pulmonary venous drainage which is, in terms of life expectancy, a most severe malformation.

SUMMARY

The gravity of prognosis, frequency, and certain of the diagnostic features of complete transposition of the great vessels have been reviewed.

It has been emphasized that the infants most desperately ill have hearts with fewer associated anomalies and are, therefore, the best candidates for surgical treatment with an eventual goal of cure in this anomaly.

We have preferred an attempt to correct complete transposition of the great vessels anatomically by transposing all of the pulmonary veins and both venae cavae to match the abnormally reversed relationships of the aorta and pulmonary artery. Evidence is suggestive that patients with such a corrected circulation are physiologically normal and might anticipate a relatively normal life expectancy in the absence of other abnormalities.

Eight patients with complete transposition of the great vessels have been operated upon to date. In the first four patients all of the right pulmonary veins were anastomosed to the right atrium. Two of these patients died, and two survived with both of the latter exhibiting significant objective and subjective improvement. This operation, alone, is not recommended, unless large internal shunts are known to exist, because of the danger of inducing rapid heart failure in those patients without adequate internal collateral shunts by unbalancing the systemic and pulmonic circulations.

In four other patients, the inferior vena cava has been shifted to the left atrium at the site of the cardiac end of the transected right pulmonary veins, the lung ends of which were anastomosed to the right atrium. None of these four patients has survived. The failures in this series of patients have been analyzed, and a remedial solution for establishing the two shunts simultaneously has been presented.

The technical aspects of these operations of realignment of the great veins have not been nearly as difficult of solution as might have been anticipated.

Adequate methods appear to be available for accomplishing complete transposition of all of the great veins without resort to grafts or other complicated methods.

Rather, our main concern has been the hazards associated with rapidly unbalancing, during the repositioning of these veins, the peculiarly independent circulations existing in complete transposition.

Acknowledgment.—We wish to express our sincere appreciation to the following members of the Pediatric Staff of the Variety Club Heart Hospital who have stimulated these efforts by their active and combined interest in these problems: Dr. Forrest Adams, Dr. Paul Adams, Dr. Ray Anderson, Dr. Robert Disenhouse, Dr. Paul Dwan, Dr. John Galligan, Dr. Robert Good, Dr. Irvine McQuarrie, and Dr. Lewis Thomas.

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DISCUSSION

DR. W. H. MULLER, JR. (Los Angeles, Calif.).—I would like to congratulate and compliment Dr. Lillehei and Dr. Varco for their beautiful presentation and for the results which they have achieved.

Dr. Frank Dammann and I have also felt that transposing the venous return rather than the aorta and pulmonary arteries in such patients is a logical and sound procedure, primarily for the reasons which Dr. Lillehei has given, the chief of which is that in a high percentage of these patients the coronary arteries arise from the aorta and cannot be transposed.

We have operated on four patients who had transposition of the aorta and pulmonary artery. Their ages ranged from 5 weeks to 6 months. Extreme hypothermia was induced during the operative procedures. In the 6-month-old patient, we found not only transposition of the arterial circulation but also pulmonary stenosis and, therefore, we performed only an anastomosis between the systemic and pulmonary circulation. In the three others, however,

we attempted to transpose partially the cardiac venous return. The superior vena cava was divided and anastomosed to the cardiac end of the superior pulmonary vein. The distal end of the superior pulmonary vein was then anastomosed to the wall of the right auricle. In one of these patients, we also transplanted the inferior pulmonary vein into the right auricle. Had our patients survived, we had hoped at a later date to anastomose the inferior vena cava to the cardiac end of the inferior pulmonary vein in a manner similar to that used by Dr. Lillehei and Dr. Varco, and possibly at a later date to perform a pneumonectomy on the left side. However, none of our patients survived longer than a few hours after operation.

DR. LILLEHEI (Closing).—It is our steadfast desire that other interested surgeons will be encouraged to attempt correction of this frequently occurring form of morbus caeruleus in spite of the high mortality associated at the moment with these endeavors. For without some form of operative management, these infants are doomed with few exceptions to an early death, the majority within the first year of life.

If one maintains an open mind, a number of interesting possibilities are apparent for achieving improvement and even cure in this condition. Our progress in this endeavor has seemed painfully slow to us, yet enough has been learned to indicate that, in those infants with transposition and with intact cardiac septa (the majority), the major problem is to achieve venous repositioning without substantially unbalancing the two basically separate circulations. I am sure that this can be done, and also that it must be done within a few minutes. That is, compensating shunts must become functional almost simultaneously.

However, in those infants with large internal shunts due to defects in the cardiac septa (this condition is easily detected at the time of surgical exploration by simply palpating a firm, hard pulmonary artery), the problem of unbalancing the two separate circulations is not nearly as acute, and one may achieve much improvement by simply transposing the pulmonary veins of the right lung to the right atrium without the compensating shunt of a vena cava being immediately necessary.

Another form of complete transposition, the type that is associated with pulmonic stenosis, should also be recognized, because these infants are frequently in trouble early in life and they do well following the performance of a classical Blalock shunt.

In reference to the question raised by Dr. Muller of where best to put the left pulmonary veins in order to return the oxygenated blood from that lung to the heart, we have made some observations at autopsy which make it appear feasible to anastomose the left pulmonary veins to the cardiac end of the divided inferior vena cava. The other possibility, if certain shunts can be accomplished so that the children are considerably improved and thus survive to older ages, is to wait until that time, and then it would be relatively easy technically to anastomose the left pulmonary veins, superior and inferior, to the coronary sinus. As far as length is concerned, the vessels are quite adequate for accomplishing either of these anastomoses.

In respect to Dr. Muller's question concerning hypothermia, cooling has not been utilized in any of these cases.

CONTROLLED UNILATERAL BRONCHOVASCULAR OCCLUSION AS A METHOD FOR STUDYING PULMONARY FUNCTION

A Preliminary Report

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THE present methods of preoperative evaluation of the patient who is a candidate for pneumonectomy are not entirely satisfactory. These methods generally consist of a study of static lung volumes (vital capacity, inspiratory and expiratory reserves), dynamic lung volumes (minute volume of ventilation, maximum breathing capacity), intrapulmonary gas mixing, and arterial blood studies (oxygen saturation, arterial carbon dioxide). In the usual case, these tests along with sound clinical judgment usually suffice in determining the patient's status. If, however, the function of the remaining lung is doubtful or if some degree of cardiorespiratory insufficiency is already present, which is frequently the situation in the pneumonectomy candidate, it would be advantageous to have a more accurate evaluation of the patient than is now obtained.

In these doubtful cases, it would, therefore, be desirable if it were possible before operation to put the patient in a state which so far as possible resembled the functional condition he would be likely to be in after operation. Realizing the shortcomings inherent in studying pulmonary function with the chest open at operation,[7] one of us (H. R. H.), in early 1951, formulated plans for occlusion of the pulmonary artery and bronchus to one lung in the intact patient.

In 1951, Carlens, Hanson, and Nordenström[1] published a report on unilateral occlusion of the pulmonary artery in dog and man, utilizing a double-lumen, balloon-tipped cardiac catheter. In three patients, they noted a slight transient rise in the main pulmonary artery pressure following occlusion for as long as twenty minutes, but no other ill effects or complications were noted.

Also in 1951, Dotter and Lukas[2] reported that an alarming increase in right ventricular pressure occurred in dogs following unilateral pulmonary artery occlusion. The average duration of the experiments was only three minutes and, in addition to the right ventricular hypertension, appreciable electrocardiographic changes occurred. One of the eight animals died. They concluded that immediate rapidly changing alterations in the hemodynamic pattern following obstruction of the unilateral pulmonary artery occurred in the intact, lightly anesthetized dog.

This work has been aided by grants from the A. Atwater Kent Fund, from the Wilson C. Laucks Memorial Foundation, and from the National Institutes of Health.

Read at the meeting of the Society of University Surgeons, St. Louis, Mo., Feb. 12-14, 1953.

In September, 1952, Carlens[3] reported that unilateral pulmonary artery occlusion had been carried out in thirty patients without any serious complications. The studies were made on patients with carcinoma, bronchiectasis, and tuberculosis in whom borderline pulmonary function was present. It was felt that this method of investigation held great promise, not only in delineating the status of the remaining lung, but also in determining the "resection tolerance" in patients with bilateral bronchiectasis and tuberculosis.

In the face of these conflicting reports on the results following unilateral pulmonary artery occlusion, our studies were instituted during the latter part of 1952.

Following preliminary experiments in dogs (Fig. 1), we occluded the pulmonary artery and corresponding bronchus to one lung in five intact, lightly narcotized patients. All five patients had bronchiogenic carcinoma and four of the five patients had subsequent thoracotomies.

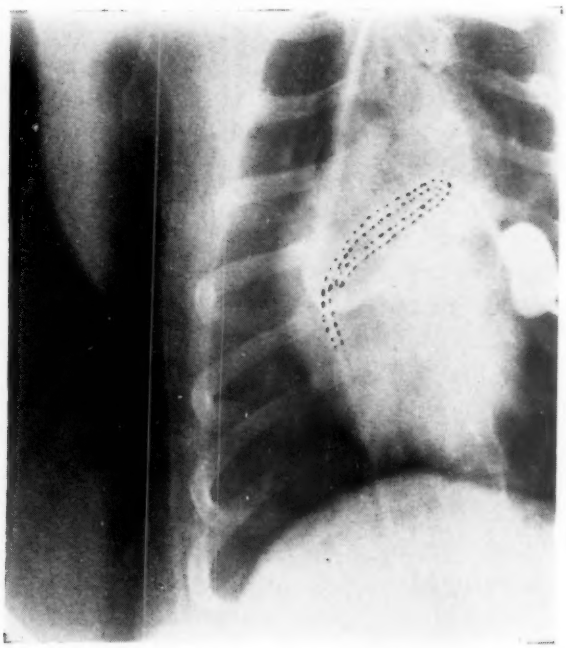

Fig. 1.—Left pulmonary artery occlusion in an anesthetized dog. The balloon used for the experimental animals was much smaller than that used for the human patients since a larger balloon would probably also occlude the main pulmonary artery. In addition to the single-lumen, balloon-tipped catheter which was passed into the left pulmonary artery through the jugular vein, a second catheter was placed into the right ventricle through the femoral vein for pressure recordings. Occlusion was for twenty minutes with no complications and no appreciable rise in right ventricular pressure. The dotted lines indicate position of second catheter.

Method of Study and Technique.—Studies have been carried out either in the operating room or in a special room adjacent to the operating suite, utilizing strict aseptic technique. Since we have not known exactly what would happen, we have tried to anticipate possible eventualities such as auricular or ventricular fibrillation or sudden cardiac standstill. Instruments for thoracotomy are at hand and a defibrillator is immediately available. An anesthesiologist and anesthesia machine are present at the head of the table.

Although we have given only small amounts of the barbiturates (pentobarbital sodium 0.1 Gm. hypodermically) for sedation, we now give also atropine or scopolamine in order to cut down on the troublesome tracheal secretions during endotracheal intubation.

The lightly sedated patient is placed on a specially built table with a treadmill attachment for graded exercise. Heparin (50 mg. intramuscularly) is given prior to catheterization, not so much because of any fear of the blood clotting distal to the occluding balloon,[4] but more especially to prevent clotting in the various catheters. The special double-lumen, balloon-tipped cardiac catheter (Fig. 2) is then inserted into an arm vein and passed under fluoroscopic guidance into the auricle, right ventricle, main pulmonary artery, and branch. Once the catheter is in position, the femoral artery is cannulated. The endotracheal catheter[5] (Fig. 2) is passed at a specified time under local anesthesia.

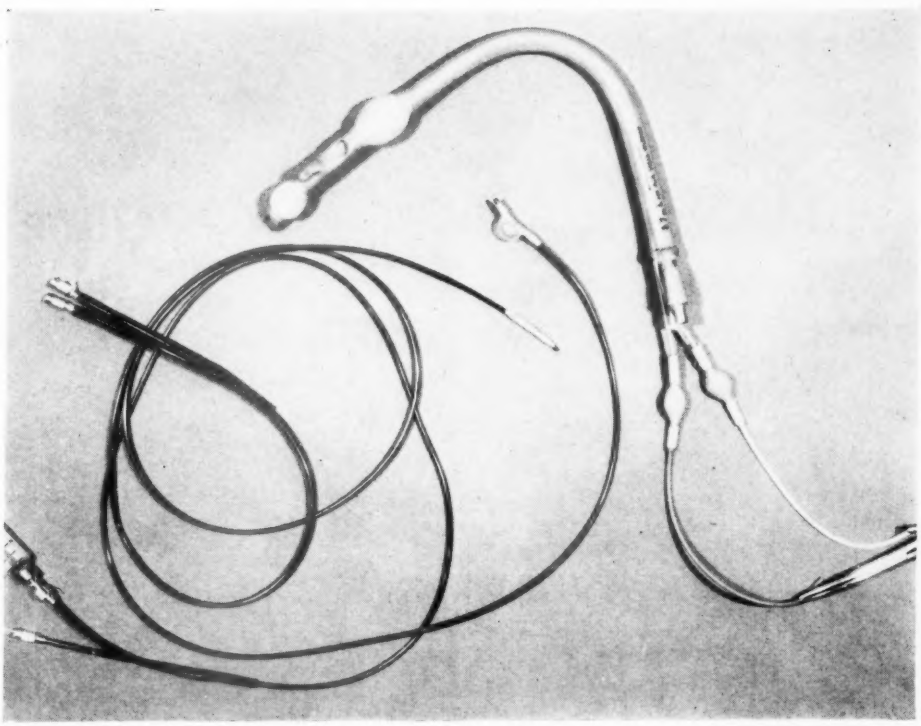

Fig. 2.—*Top*, A Carlens-Stille endotracheal tube, a hard-rubber, double-lumen tube with two inflatable cuffs. Each lumen has an internal diameter of 7 millimeters. *Bottom*, Radiopaque double-lumen cardiac catheters, 125 cm., size eight and one-half. The balloon is continuous with one of the lumina, the other lumen opening proximal or distal to the balloon.*

Studies made are as follows: Continuous main pulmonary artery and femoral artery pressures are recorded on the Sanborn Polyviso recorder through a Lilly capacitance manometer. Zero reference level for intracardiac pressures was 8 cm. above the spine of the supine patient. Continuous electrocardiographic tracings are made, as are serial blood gas analyses on mixed venous and

*Obtained from United States Catheter and Instrument Corporation, Glens Falls, N. Y.

arterial blood,[6] at varying intervals prior to and following bronchovascular occlusion. The roentgenograms shown in Figs. 3 and 4 were taken at the time of unilateral bronchovascular occlusion in two patients. In Fig. 4 the endotracheal catheter is clearly visible.

Complications.—In one patient the temperature rose to 105° F. one hour following conclusion of the procedure, but it had returned to normal in three hours. The patient suffered no ill effects other than the temperature elevation. We feel that this probably represented a reaction to the perfusion fluid. There have been occasional extrasystoles as the catheter passed through the right ventricle, but otherwise there were no complications or untoward sequelae.

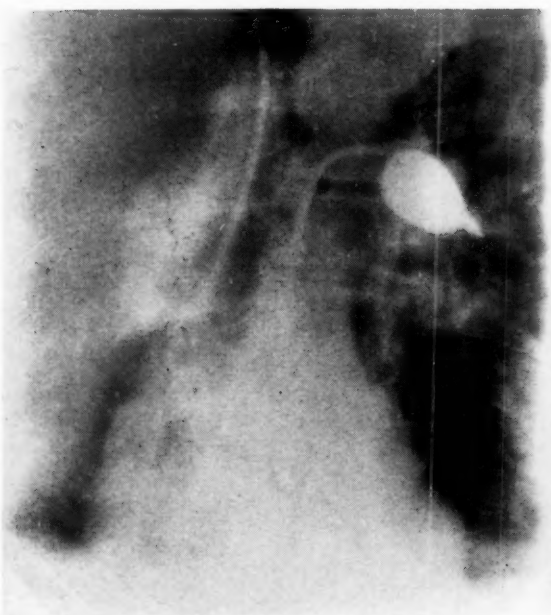

Fig. 3.

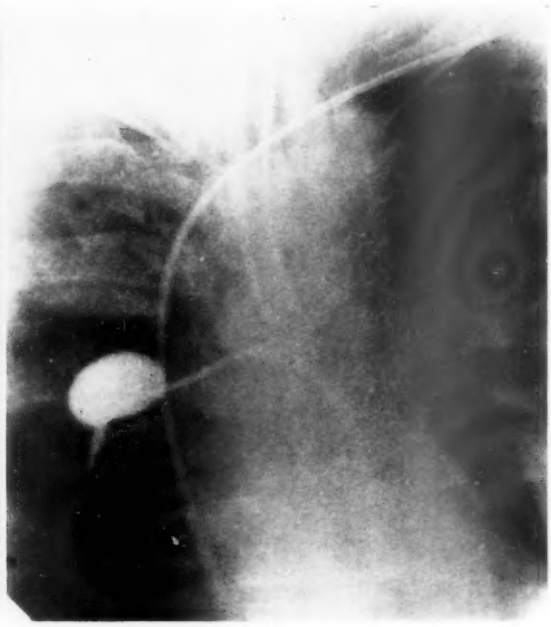

Fig. 4.

Fig. 3.—Patient G. C., a 68-year-old man with carcinoma of the left lung. The left pulmonary artery was occluded for thirty minutes and the left main-stem bronchus for eight minutes.

Fig. 4.—Patient G. P., a 61-year-old man with carcinoma of the right lung. The right pulmonary artery was occluded for fifty-five minutes and the right main-stem bronchus for twenty minutes. Note that the endotracheal catheter is clearly shown in position.

Results and Discussion.—Pulmonary artery occlusion has ranged from thirty to sixty minutes, with an average time of forty-four minutes. The corresponding bronchial occlusion has been from eight to thirty minutes, with an average of sixteen minutes. Completeness of bronchial occlusion has been indicated by absence of breath sounds on the involved side and absence of motion of the chest and diaphragm on the involved side. We could not be sure of the completeness of arterial occlusion in every case. However, 6 ml. or more of 35 per cent Diodrast was used in every case. Since Carlens and associates[1] showed evidence of complete occlusion (with angiocardiograms) with 4 or 5 ml., we feel reasonably certain that the arteries were

occluded with the larger amount. Also, in the last patient, pressure recordings distal to the occluding balloon were at the base line, indicating that in this patient, at least, occlusion was complete.

Main Pulmonary and Femoral Artery Pressures.—There has been a slight to moderate elevation of the main pulmonary artery pressure to between 4 and 8 mm. Hg following occlusion of one branch. In no instance, however, did we get the alarming increases reported by Dotter and Lukas in their animals.

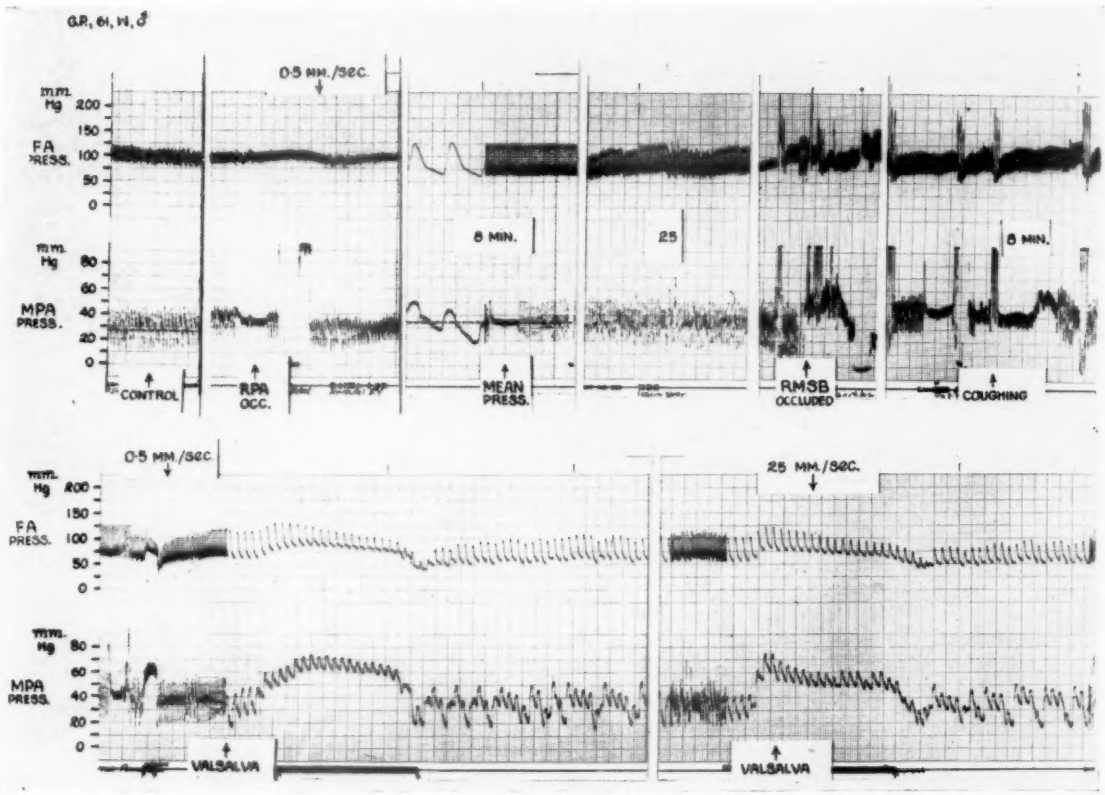

Fig. 5.—Pressure tracings in main pulmonary artery (*MPA press.*) and femoral artery (*FA press.*). *RPA occ.* represents right pulmonary artery occlusion; *RMSB occluded* represents right main-stem bronchus occluded. (See text.)

Fig. 5 is representative of three of the five patients who had normal control pulmonary artery pressures. The remaining two patients had elevated control pressures and are discussed subsequently. Note in Fig. 5 that the mean control resting main pulmonary artery pressure was 26 mm. Hg. There was no immediate rise in pressure, but eight minutes later the pressure had risen to 34 mm. Hg and, at twenty-five minutes, remained at that level. No appreciable change occurred in the femoral artery pressure. Thirty-five minutes after right pulmonary artery occlusion, the right main-stem bronchus was occluded. Incident to the coughing, there was an increase in the pulmonary artery pressure, but note that at eight minutes following occlusion of the bronchus it had leveled off to around 38 to 40 mm. Hg mean pressure.

The bottom graphs in Fig. 5 show the results of the Valsalva maneuver after occlusion of the artery alone (lower left tracing) and after occlusion of the right main-stem bronchus (lower right tracing). A typical femoral arterial pressure response was demonstrated, and a response regarded by Cournand as normal for the right ventricle[7] was obtained in the main pulmonary artery.

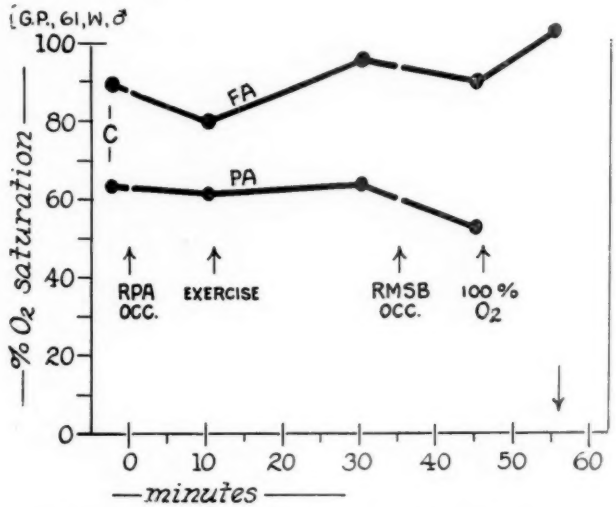

Fig. 6.—Oxygen saturation studies on Patient G. P. (See text.) *C* represents control; *FA*, femoral artery; *PA*, pulmonary artery; other abbreviations same as in Fig. 5.

Serial Gas Analysis Determinations.—Fig. 6 shows the oxygen saturation studies on Patient G. P. This patient was the only one heavily sedated prior to the procedure, and was the only one of the five showing any appreciable change in the arterial oxygen saturation following occlusion of the pulmonary artery. That this reduction was probably due to the sedation is indicated by the fact that twenty minutes following exercise the arterial oxygen saturation had returned to the control level. Following occlusion of the main-stem bronchus, however, there was an appreciable decrease in arterial oxygen saturation. Definitive interpretation of this latter phenomenon must await further experience since several factors could have conceivably contributed to the decrease. Corollary experiments utilizing the method of airflow resistance have indicated that some degree of stenotic breathing does occur with the endotracheal catheter which we have used.[8] Troublesome tracheobronchial secretion occurring at the time of intubation has been another factor in two of the patients. Third, as will be seen from evidence presented later in the article, it may be that in two of the patients the decrease in arterial oxygen saturation was a result of impaired pulmonary function in the remaining lung. Note in Fig. 6 that the oxygen saturation returned to normal levels following inhalation of 100 per cent oxygen for five minutes.

Electrocardiographic Changes.—In no case has there been any appreciable alteration of the electrocardiogram during the entire duration of the respec-

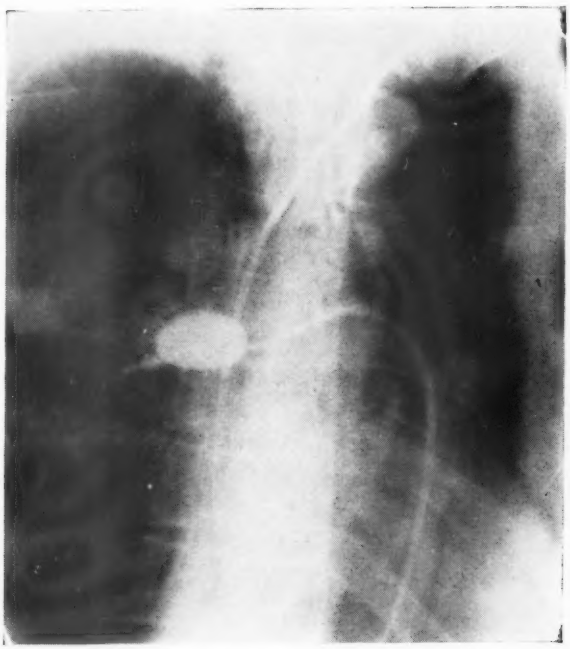

Fig. 7.—Patient P. M., a 66-year-old man. Right hydropneumothorax and almost complete collapse of right lung. This patient proved to have a carcinoma of the lung with metastasis to the parietal pleura. Right pulmonary artery occlusion was for thirty-five minutes, and the right main-stem bronchus was occluded for ten minutes.

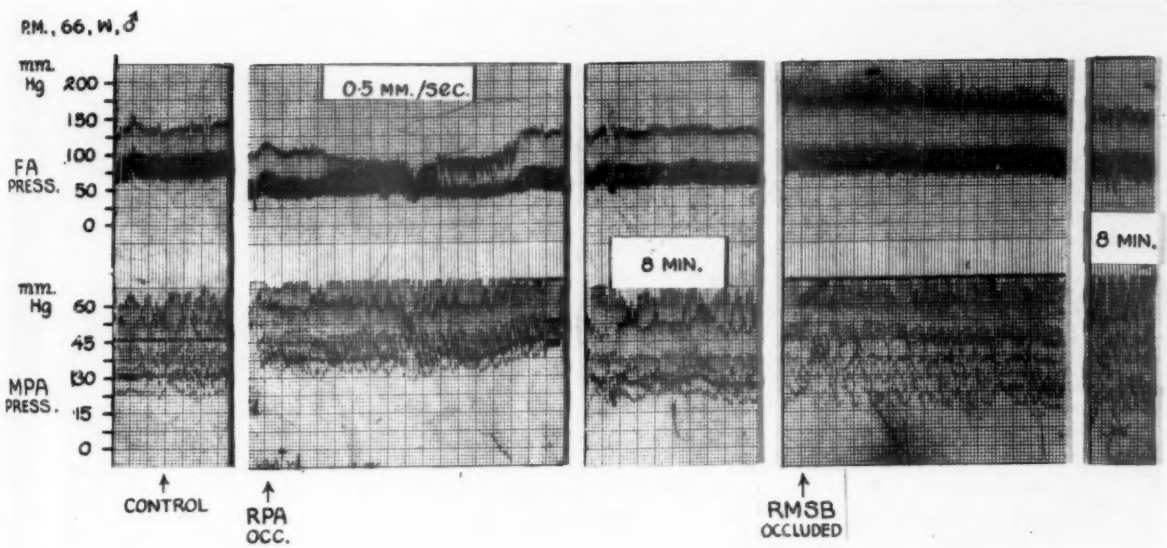

Fig. 8.—Pressure tracings on Patient P. M. The control main pulmonary artery pressure is 46 mm. Hg. Abbreviations same as in Fig. 5.

tive studies. As stated, occasional extrasystoles were noted as the catheter passed through the right ventricle, but there were no other alterations of rhythm. There was never any suggestion of tracings which might be indicative of a pulmonary embolus.

The remaining two cases are of special interest.

Fig. 9.—Patient G. B., a 62-year-old man with carcinoma of the right lung. Right pulmonary artery was occluded for sixty minutes and right main-stem bronchus for thirty minutes.

P. M., a 66-year-old white man, was admitted to the hospital with extreme dyspnea on only slight exertion for approximately ten months. Roentgen examination revealed a hydropneumothorax on the right and almost complete collapse of the right lung. There was a mass projecting from the antero-inferior aspect of the collapsed lung on lateral projection. Following thoracentesis, study was carried out and the catheter was passed into the right pulmonary artery (Fig. 7). The right pulmonary artery was occluded for thirty-five minutes and the right main-stem bronchus for ten minutes.

Analysis of the pressure patterns (Fig. 8) revealed a mean control resting main pulmonary artery pressure of 46 mm. Hg which rose to 54 mm. immediately following occlusion. However, at eight minutes the pressure had returned to control levels and was not appreciably altered following right main-stem bronchial occlusion.

Exploratory thoracotomy was carried out. There were 250 to 300 ml. of serosanguineous fluid in the right chest, and carcinomatous implants were spread diffusely over the parietal pleura. The right lung was completely trapped with a thick visceral peel. Decortication was performed in the hope that it might relieve the patient's dyspnea. Following freeing of the lung, a mass could be felt in the lower lobe near the hilus, and it was felt that this represented the primary lesion. Following decortication, also, pulmonary artery pressure was taken through a No. 18 needle and was found to be 5 cm. of blood.

For all functional purposes this patient had already created upon himself a "pneumonectomy." The right lung was almost completely atelectatic.

As Björk and Salen[9] and Burford and Webb[10] have shown, and as was revealed at operation in this case, the blood flow through the involved lung was markedly decreased and the left lung was already carrying the full load. Since a normal single lung is capable of carrying three to four times the amount of blood normally coursing through it without elevation of the main pulmonary artery pressure,[11] it is reasonable to assume that pulmonary function in the remaining lung in this patient was not adequate to take the increased load and pulmonary hypertension developed. Since there was practically no blood flowing through the atelectatic lung, one would not anticipate a further appreciable rise in main pulmonary artery pressure following occlusion.

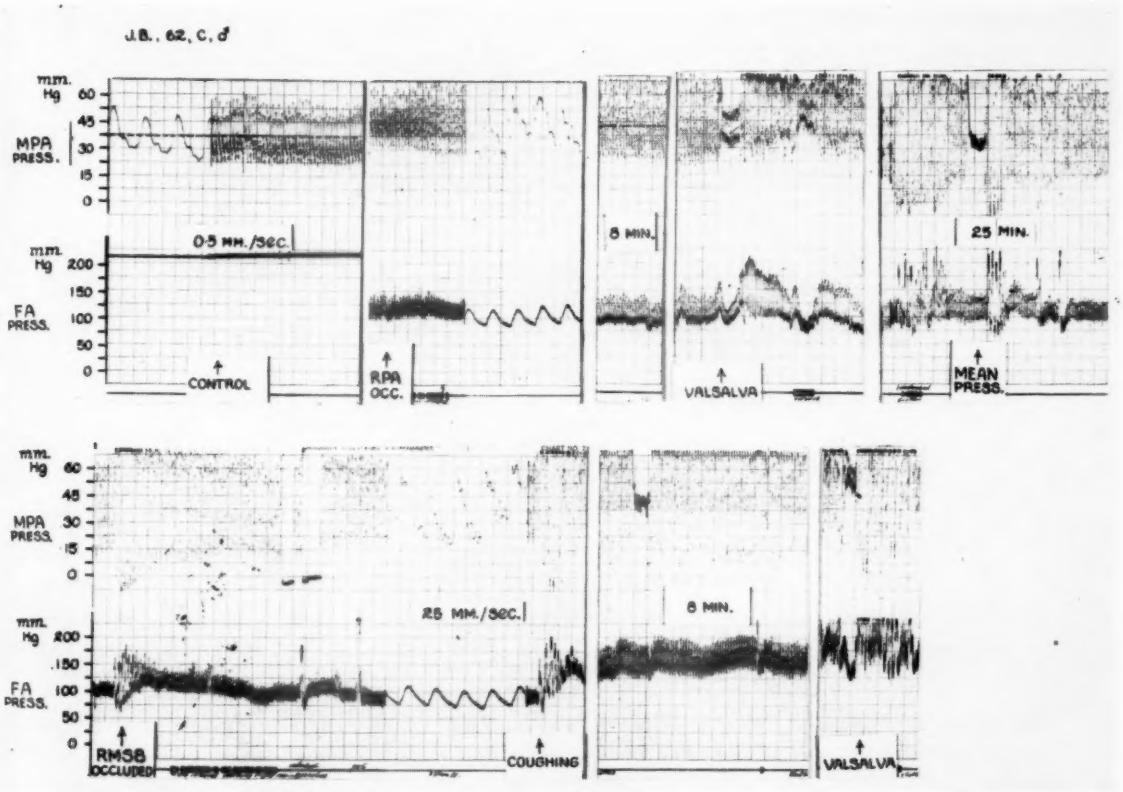

Fig. 10.—Femoral and pulmonary artery pressures in Patient G. B. (See text.) Note that, while the femoral arterial response to the Valsalva maneuver is similar to that in Fig. 5, the pulmonary arterial response is not at all similar. There is a decrease in the systolic and pulse pressures, and an increase in the diastolic pressure. Abbreviations same as in Fig. 5.

Following decortication and re-expansion of the right lung, the patient's dyspnea was definitely improved. It is unfortunate that we were unable to get postoperative pulmonary artery pressures.

G. B., the other patient, was a 62-year-old man with roentgen findings of a large mass in the hilum of the right lung. There had been no dyspnea. Catheterization studies were performed (Fig. 9). The right pulmonary artery was occluded for sixty minutes and the right main-stem bronchus for thirty minutes.

The control resting main pulmonary artery pressure was 37 mm. Hg (Fig. 10) and at eight minutes after occlusion it had risen to 42 mm. Hg. At twenty-five minutes it had returned to approximate control levels. Eight minutes following right main-stem bronchus occlusion, the pressure had risen again to 42 mm. Hg.

Oxygen saturation studies (Fig. 11) showed no change following arterial occlusion, a fall following right main-stem bronchus occlusion, and return to normal with 100 per cent O_2.

At operation, a right pneumonectomy was performed. The patient had a smooth postoperative course and was discharged on the fourteenth day. Since leaving the hospital, however, he now becomes dyspneic on only slight exertion. He volunteers that he is much more short of breath than before operation. Further studies are in progress on this patient.

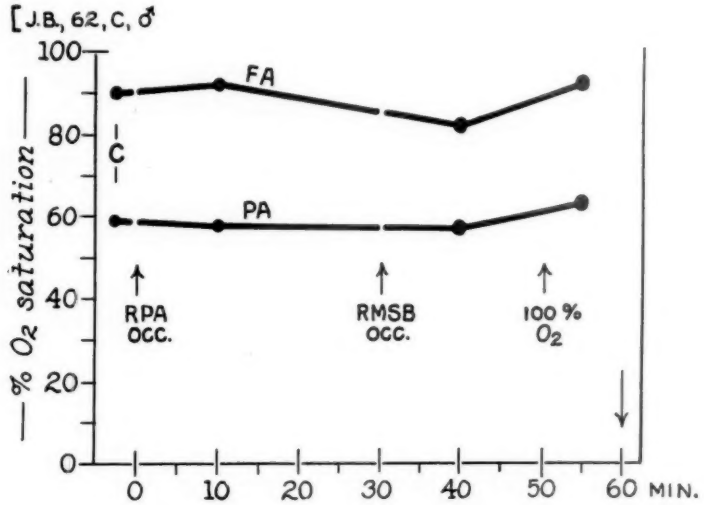

Fig. 11.—Oxygen saturation studies in Patient G. B. Note the appreciable fall following right main-stem bronchus occlusion and the return to normal value with 100 per cent oxygen. Abbreviations same as in Fig. 5.

In the light of the subsequent course, a careful analysis of the pressure curves (Fig. 10) may have greater significance than merely as an indication of the presence of pulmonary hypertension. The response to the Valsalva maneuver was puzzling. Note that there was a typical femoral artery response but, instead of the expected response in the main pulmonary artery, there was a decrease in the systolic pressure, a decrease in the pulse pressure, and an increase in the diastolic pressure. The significance of this observation in this single case is not yet clear, but Dotter and Lukas have interpreted this phenomenon as representing beginning acute failure of the right ventricle. It may be that in this patient the remaining lung was just able to carry the increased load following right pulmonary artery occlusion, but when, on top of this, main pulmonary artery pressure was further increased by the Valsalva maneuver, then the right ventricle began failing. This may have been a clue to the patient's decreased tolerance to exercise following pulmonary resection.

CONCLUSIONS

1. Unilateral occlusion of the pulmonary artery has been accomplished for as long as sixty minutes without any untoward sequelae.

2. There is a slight to moderate rise in the pulmonary artery pressure following occlusion, but never to the alarming proportions reported by Dotter and Lukas. Thus far, our experiments have confirmed the findings of Carlens and his group in this respect.

3. There has been correlation between main pulmonary artery pressure and dyspnea.

4. Alterations in serial gas analysis determinations may be correlated with variations encountered in the main pulmonary artery pressures.

5. No appreciable alterations have occurred in the electrocardiographic tracings.

6. We feel that this method will prove to be a very useful tool, not only for studying pulmonary function and pulmonary physiology, but also for studying lung vasculature and in radiologic diagnosis. By injecting contrast media distal to the occluding balloon, individual lung vascular bed studies may be made without the necessity for rapid serial exposures.

Acknowledgments.—We are grateful to Dr. Arthur Finkelstein, Director of the Department of Radiology, and to Dr. Robert Roy and Dr. Anthony Jose of his staff for the roentgen aspect of the study. Dr. Aaron Heisen, of the Department of Cardiology, has developed the electrocardiographic aspect of the problem.

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PROGRESSIVE INFANTILE EMPHYSEMA

A Surgical Emergency

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RESPIRATORY emergencies are a very frequent cause of death in the neonatal period and infancy. Compiled statistics obtained from the Obstetrical Service at the University of Iowa Hospitals over the two-year period, 1950 and 1951, showed a total stillborn and neonatal death rate of 3.2 per cent. Of those reported deaths, 31 per cent were attributed to varied pulmonary causes. Some of those emergencies cannot be subjected to remediable measures. However, a group of patients with localized, rapidly progressive emphysema are salvable if this condition is recognized in time and promptly treated.

This syndrome was first mentioned by Koontz[7] in 1925 in a publication dealing with congenital cysts of the lung. It is a collective review of the then-available cases and it includes a report of a 15-day-old child who had succumbed to the condition under discussion. Caffey[3] and Maxwell[9] each report cases of patients who showed spontaneous regression of localized emphysematous areas. They stress the fact that those changes are due to intermittent bronchial obstruction accompanying episodes of pneumonitis. The first successful pulmonary resection in an infant for tension cysts was reported in 1943 by Fischer and colleagues.[4] Further reports of resections in infants have been published by Gross,[6] Burnett and Coswell,[2] Leahy and Butsch,[8] Strode,[13] Ravitch and Hardy,[10] Griffin and colleagues,[5] Robertson and James.[11] The last three reports published in 1952 were by Shaw,[12] Whitesell and White,[14] and Williams.[15]

In all the reported instances as well as in the cases of patients observed and treated by us, the symptomatology has presented a fairly uniform pattern irrespective of whether it is due to localized congenital cystic disease or obstructive emphysema. The symptoms of progressive dyspnea and cyanosis are produced by the pathophysiology of a rapidly expanding intrapleural lesion. The expanding pulmonary segment or lobe may reach many times its normal size. By mere expansion the surrounding normal lung tissue as well as the contralateral lung will become atelectatic. Shift of the mediastinal structures including the heart, depression of the diaphragm, and ultimate development of an emphysematous rib cage contour are commonly observed. This train of events if not interrupted will lead to a rapid anoxic death.

During the past eighteen months, we have seen and surgically treated the patients in the following four case reports. They represent examples of the syndrome under discussion.

Read at the meeting of the Society of University Surgeons, St. Louis, Mo., Feb. 12-14, 1953.

CASE REPORTS

CASE 1.—M. S., a 5-month-old white male infant, was admitted to the University of Iowa Hospitals on June 10, 1951, with the complaint of increasingly severe dyspnea, more so for the last two days. Ever since birth the patient had a grunting type of rapid respiration, and there have been several episodes of upper respiratory infections, the last one having occurred two months before admission. No cough, stridor, or cyanosis has been present. Physical examination revealed an infant in severe respiratory distress. The chest cage had an emphysematous contour. Tracheal and mediastinal shift to the right and reduced breath sounds in the left hemithorax were noted. A roentgenogram of the chest revealed the heart and mediastinal structures to be displaced into the right hemithorax. An extremely emphysematous left lung containing bullae in the left upper lung field was present. The latter produced a large anterior mediastinal herniation of the lung. The left diaphragmatic leaf

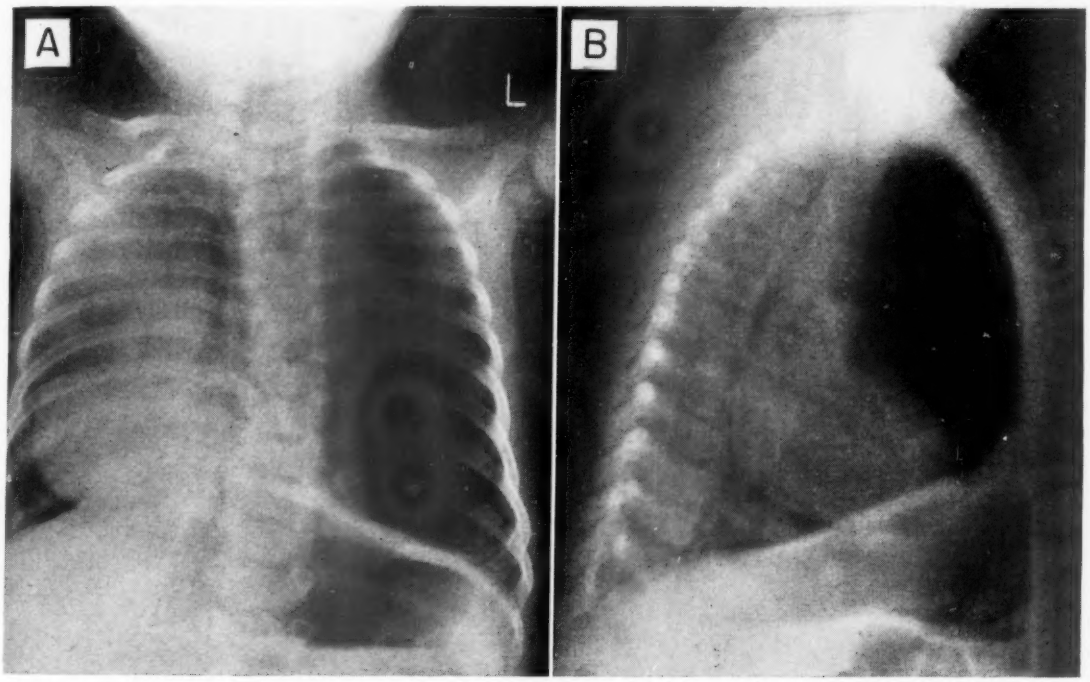

Fig. 1 (Case 1).—Preoperative posteroanterior (*A*) and lateral (*B*) roentgenograms of the chest. Emphysema of the left upper lobe, shift of the mediastinal structures, depression of diaphragm, and anterior mediastinal hernia are demonstrated.

was depressed and flattened and attenuation of the left main-stem bronchus was noted (see Fig. 1). Blood count and urine examination were within normal limits. During the first twelve hours of the baby's hospital stay, his condition deteriorated rapidly, leading to emergency thoracotomy on June 11, 1951. The left upper lobe was hugely enlarged. The anterior segment was replaced by multiple cystic blebs, producing atelectasis of the remaining normal lung tissue. A segmental resection by individual ligation technique of the involved area was carried out. Upon examination of the specimen, the bronchus as well as the segmental vessel was found to be smaller than that to the adjacent segments. Microscopic examination of the lung parenchyma revealed many large and small cystic areas lined by tall columnar epithelium. Intervening areas of atelectatic lung parenchyma were present (see Fig. 2). No endobronchial obstructions could be demonstrated. The pathologic diagnosis was congenital cystic disease of the lung involving a portion of the left upper lobe. The postoperative course was uneventful, and the child was discharged on the eighth postoperative day in good condition. A roentgenogram of the chest showed a healthy postoperative appearance.

Comment.—This patient represents an acute respiratory emergency due to apparently localized congenital cystic disease involving a portion of the left upper lobe. Surgical treatment was carried out successfully by segmental resection of the involved area.

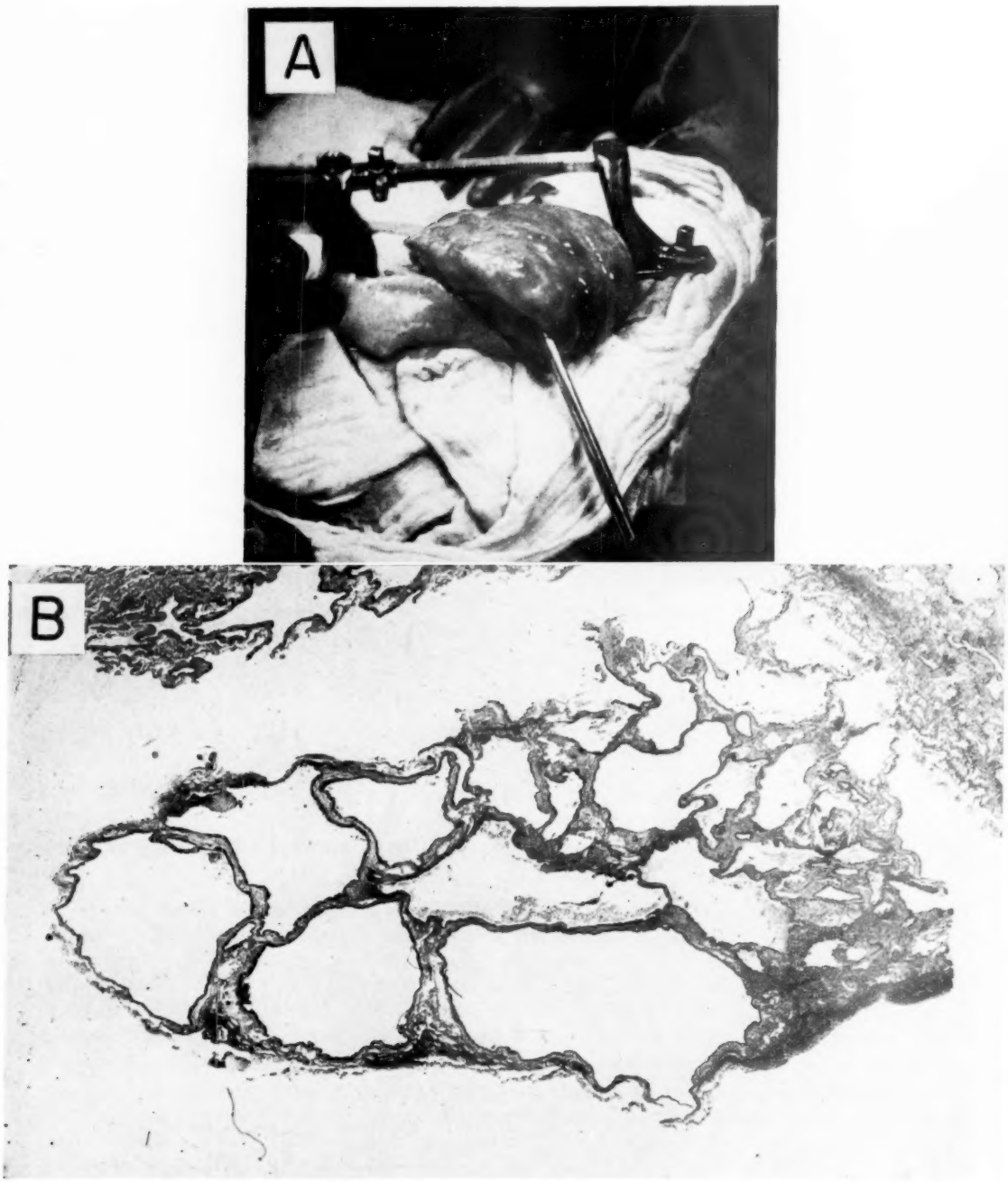

Fig. 2 (Case 1).—*A*, Photograph at time of left thoracotomy, showing the bulging cystic left upper lobe and the compressed normal left lower lobe of the lung. *B*, Photomicrograph demonstrating an area of congenital cystic disease.

CASE 2.—C. C., a 4½-month-old female infant, was admitted to the University of Iowa Hospitals on Aug. 13, 1951, with the complaint of cough, vomiting, and increasing dyspnea. Pregnancy and delivery were uneventful. At the time of birth the child weighed three and one-half pounds. Prolonged and forceful respiratory measures had to be employed to resuscitate the infant. The child remained cyanotic except when kept in oxygen. Since then, more frequent and severe episodes of coughing, dyspnea, and cyanosis finally led to hospitalization. At the age of 4 months the baby weighed eleven pounds and showed underdevelopment and great irritability.

The positive findings on physical examination at the time of admission consisted of cyanosis, an inspiratory and expiratory stridor, and marked supraclavicular and subcostal retraction during respiration. The lungs were clear on auscultation. Laboratory findings were within normal limits except for evidence of hypochromic anemia.

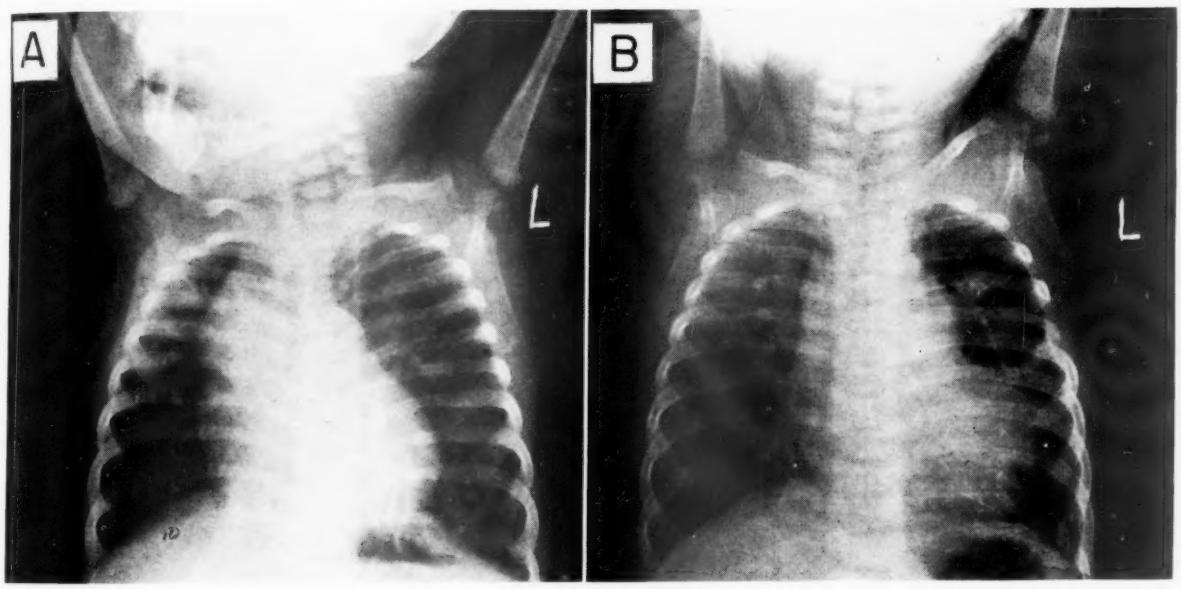

Fig. 3 (Case 2.)—Preoperative (*A*) and postoperative (*B*) roentgenograms of the chest showing generalized emphysematous changes. Preoperative mediastinal displacement to the right and postoperative restoration to normal are demonstrated.

Roentgenograms of the chest showed a density in the right upper lung field. Emphysema involving the left upper lung field was noted. There was no tracheal compression. Progress roentgenograms of the chest showed rapid progression of the emphysema of the left upper lobe with herniation of this lobe through the anterior mediastinum (Fig. 3). Roentgen therapy was given to the thymic region without benefit. On Aug. 30, 1951, a left thoracotomy with segmental resection of the apical and anterior segments of the left upper lobe was carried out. These areas were the site of the most severe emphysematous change which produced the marked mediastinal displacement and atelectasis of the remaining pulmonary tissue. Some mild emphysema was noted throughout the remainder of the lung. Pathologic examination of the removed tissue revealed emphysema without evidence of cystic disease (see Fig. 4). No localized bronchial abnormalities were found. The postoperative course was uneventful. The respiratory symptoms and cyanosis disappeared. The child was discharged in good condition on Oct. 2, 1951. The baby was readmitted on Nov. 6, 1951, because of recurrence of respiratory difficulties and a severe stridor. Roentgenograms at this time revealed marked emphysema of the entire left remaining lung tissue as well as of the right lower lobe. Supportive measures were given, and the child was discharged on Nov. 19, 1951. The child died in another hospital on Dec. 10, 1951. The autopsy findings were reported as those of diffuse cystic disease.

Comment.—This child presents an example of progressive respiratory difficulty finally leading to death on the basis of diffuse pulmonary emphysema. Temporary amelioration of symptoms resulted from resection of the most severely involved pulmonary segments. Pathologic examination of the surgically removed pulmonary tissue did not bear out the diagnosis of congenital cystic disease. Overly energetic and prolonged resuscitative measures at the time of birth may have been a causative factor in the production of the emphysema.

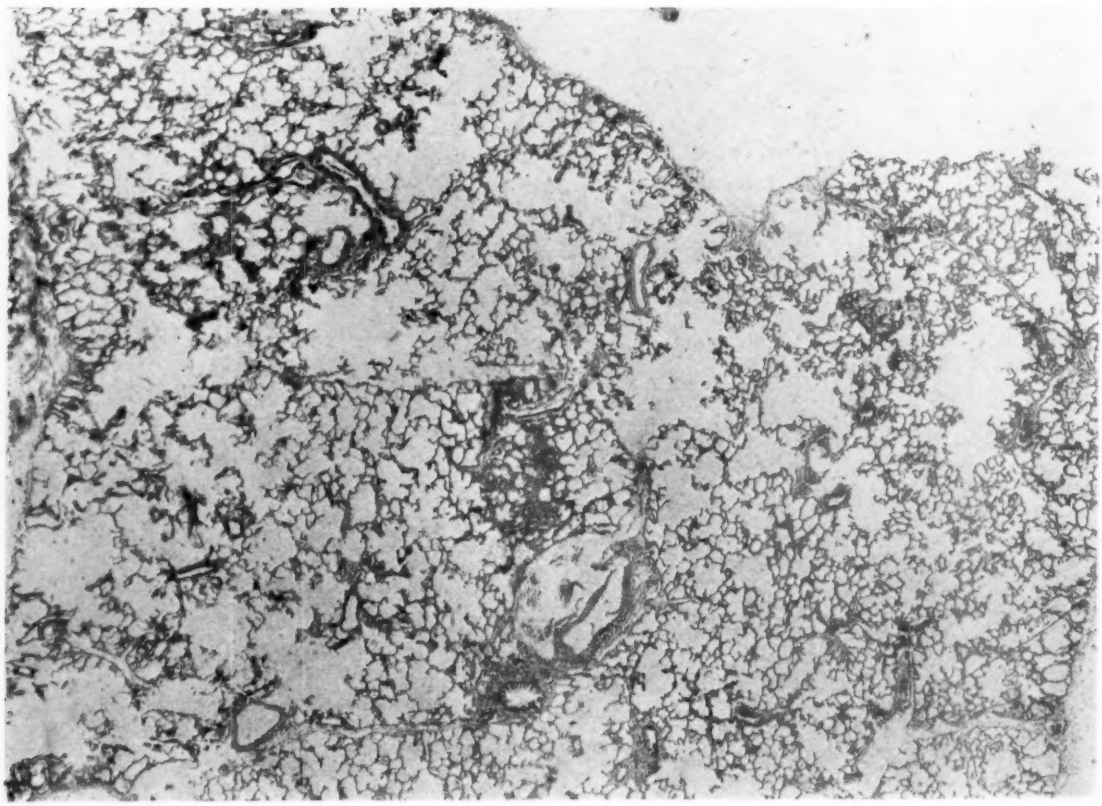

Fig. 4 (Case 2).—Photomicrograph demonstrating pulmonary emphysema with fragmentation of alveolar septa.

CASE 3.—N. W., a 12-day-old female infant, was admitted to the University of Iowa Hospitals on Feb. 11, 1952, with the complaint of dyspnea and cyanosis. The child's mother stated that the pregnancy and delivery were uneventful. At birth the child weighed eight pounds six ounces and cried immediately. It was noted that the baby's fingers were cyanotic. No resuscitative measures needed to be employed. On the second day of life, the child's cyanosis became very marked necessitating continuous oxygen administration. The presumptive diagnosis of agenesis of the left lung had been made prior to admission to the University Hospitals. Physical examination revealed a normally developed 2-week-old infant, markedly cyanotic and dyspneic. The right hemithorax was emphysematous and bulging. There was marked retraction of the supraclavicular and subcostal areas during the rapid respiratory efforts. Breath sounds were audible on the left side. Blood count and urinalysis were within normal limits. Roentgenograms of the chest demonstrated a large emphysematous area in the right lung field with herniation through the anterior mediastinum as well as shift of the heart to the left and compression atelectasis of the contralateral lung.

A roentgenogram on March 4, 1952, revealed further progression of the previously mentioned findings (Fig. 5). On the same date a right thoracotomy was carried out. The right middle lobe was found to be extremely emphysematous and many times its normal size, displacing and compressing the surrounding lung and mediastinal structures. A right middle lobectomy was carried out. Pathologic examination of the resected middle lobe revealed the bronchus to be of normal width but slitlike in configuration. No endobronchial valves or obstructions were found. The cartilage and the bronchial mucosa appeared normal. The lung parenchyma on section showed emphysema without evidence of cystic disease (Fig. 6). The postoperative course was uneventful, and the child was discharged on March 14, 1952. A healthy postoperative chest was seen on the roentgenogram. The baby was seen again during May and September, 1952, and both times the infant appeared to be normal.

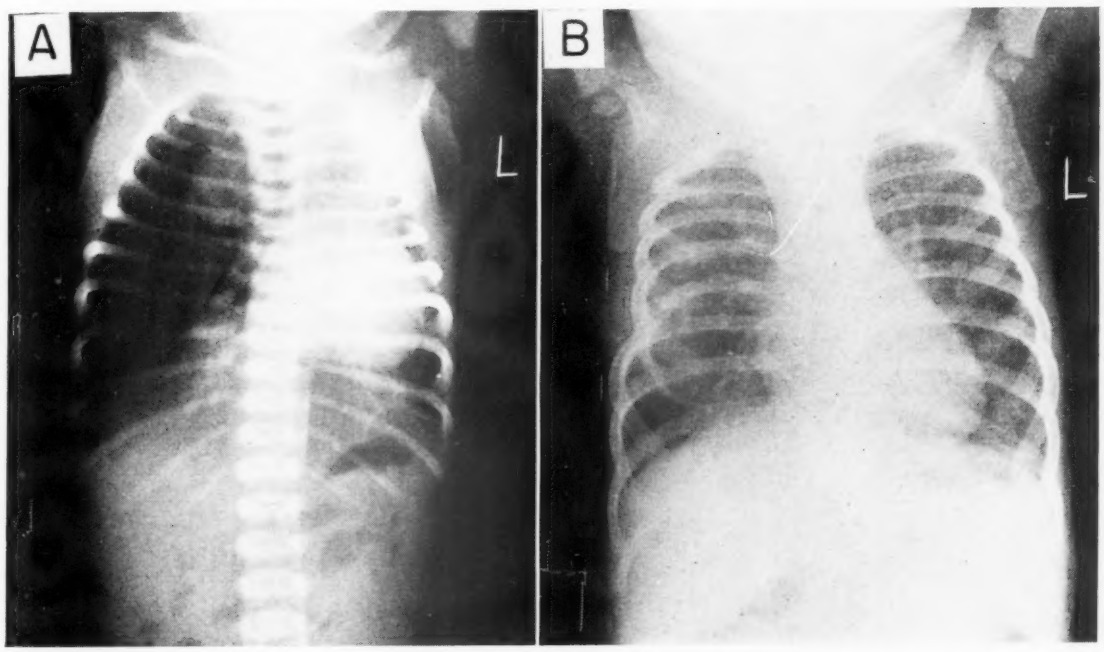

Fig. 5 (Case 3).—Preoperative (*A*) and postoperative (*B*) roentgenograms of the chest demonstrating restoration of normal conditions following resection of the emphysematous right middle lobe.

Comment.—This 2-week-old infant demonstrates an example of localized, rapidly progressive emphysema of the right middle lobe producing a respiratory emergency which started immediately after birth. There was no evidence of congenital cystic disease.

Case 4.—J. McG., a 16-day-old female infant, was admitted to the University Hospitals on Aug. 21, 1952, with the complaint of marked dyspnea and cyanosis. The mother had an uneventful pregnancy and labor. The child weighed six pounds four ounces at birth and was not cyanotic. One week after birth, the child uttered a piercing cry and was noted to become progressively cyanotic. Roentgenograms of the chest taken at that time by the local physician were said to show atelectasis of the left lung. Intratracheal intubation was carried out and positive pressure oxygen was given in an attempt to "expand the collapsed left lung." Physical examination at the time of admission revealed a dehydrated, thin, cyanotic infant in acute respiratory distress. Subcostal and supraclavicular retractions were noted on inspiration. The right hemithorax was bulging and emphysematous. Urinalysis and blood findings were within normal limits. Roentgenograms of the chest twenty-four hours following the initial examination demonstrated a rapidly progressing emphysema of the

right middle lobe with a large anterior mediastinal lung hernia and displacement of the mediastinal structures and heart to the left (Fig. 7). At the time of right thoracotomy on Aug. 22, 1952, a very emphysematous and greatly enlarged right middle lobe was encountered. A right middle lobectomy was carried out. The pathologic examination demonstrated a normal bronchial tree without evidence of endobronchial obstruction. Sections of the lung parenchyma showed generalized emphysema with patchy areas of atelectasis and no evidence of congenital cystic disease (Fig. 8). The child was discharged on Aug. 28, 1952, after an uneventful postoperative course. Roentgenogram at that time revealed a normal postoperative chest.

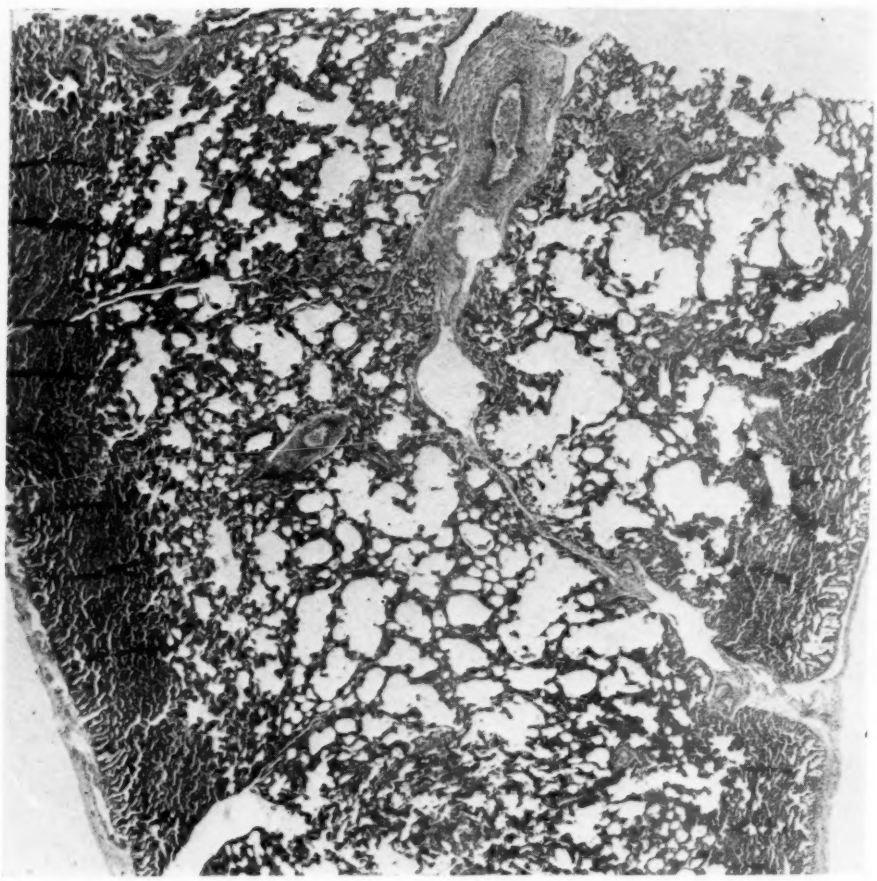

Fig. 6 (Case 3).—Photomicrograph demonstrating emphysematous changes and atelectasis of some of the adjacent pulmonary parenchyma.

Comment.—This 2-week-old infant was believed prior to admission to suffer from an atelectatic left lung. The respiratory difficulties were progressive leading to emergency thoracotomy and resection of an emphysematous right middle lobe. Forceful insufflation with tracheal intubation was carried out after the onset of more marked and progressive symptoms one week following birth and shortly prior to thoracotomy. The offending right middle lobe demonstrated only emphysema.

Causative Factors.—Several mechanisms have been suggested as the causative factors of the process under discussion. A check valve effect involving a

lobar or segmental bronchus producing obstructive emphysema of lung parenchyma supplied by this bronchus is a plausible explanation. This check valve may be due to actual mucosal folds, as described by Robertson and James[11] in one of their cases, or it may be due to an obstructing foreign body or a mucous plug during pulmonary infectious episodes. Localized chondromalacia of the bronchial rings or absence of bronchial supporting cartilage has been suggested by Shaw.[12]

One patient (Case 3) did show an unusually narrow and slit-like bronchus which might easily have become obstructed during the expiratory phase of respiration, trapping air and producing progressive localized obstructive emphysema. The bronchus, however, did show normal cartilaginous rings on pathologic examination. The other three patients reported showed no evidence of obstructive endobronchial processes. Bronchi and pulmonary parenchyma altered by congenitally faulty development including anomalous vascular supply producing large parenchymal cystic areas have been described by Koontz,[7] Gross,[6] Adams,[1] and Ravitch and Hardy.[10] One of our reported patients (Case 1) clearly demonstrates this latter concept to be one of the etiologic factors. None of our patients demonstrated anomalous pulmonary vessels. In the publications by Robertson and James[11] and the one by Shaw[12] mention is made of the possible role in the production of emphysema by vigorous resuscitative measures in the neonatal period. This seems to us a very significant cause. Most of the patients reported had unusually vigorous and sometimes prolonged respiratory assistance or resuscitative measures.

To further illustrate this point, we are reporting the following four patients.

CASE 5.—Baby S. was born on Sept. 14, 1947, following an uncomplicated term pregnancy. Delivery was spontaneous. Asphyxia was noted at birth, which was treated by forceful mouth-to-mouth breathing and use of a Flagg resuscitator. The infant did fairly well for a few hours but was found dead in the crib twenty hours after birth. Post-mortem examination revealed extensive alveolar, mediastinal, and interstitial pulmonary emphysema. Microscopic examination confirmed the gross pathologic findings (Fig. 9).

CASE 6.—Baby H., a male infant, was born one month premature on Oct. 10, 1949, following an otherwise normal pregnancy. Delivery was spontaneous, lasting three hours. The child was cyanotic at birth. Resuscitative measures including forced oxygen insufflation through an intratracheal tube were carried out without improvement. The child was pronounced dead two hours following delivery. Post-mortem findings demonstrated extensive pulmonary and mediastinal emphysema and a complete pneumothorax on the right. Histopathologic examination confirmed the gross post-mortem findings (Fig. 10).

CASE 7.—R. P., a 4-month-old male child, was born prematurely June 12, 1952, following a seven-month gestation period. The delivery was spontaneous. After extensive resuscitative efforts the baby was placed in an air-lock resuscitator. The child remained in oxygen in the local hospital until admission to the University Hospitals on Oct. 17, 1952. At this time the history of severe respiratory difficulty since birth was obtained. Attempts to demonstrate the presence of a tracheo-esophageal fistula or compression of the trachea by anomalous vessels were carried out using Lipiodol studies. Roentgenograms of the chest revealed marked bilateral emphysema and there were suggestive findings of an aberrant right subclavian artery. The respiratory symptoms increased. A left exploratory thoracotomy was carried out. At operation the only finding was diffuse pulmonary emphysema. Postoperatively the child did poorly and died on the nineteenth postoperative day. Post-mortem examination confirmed

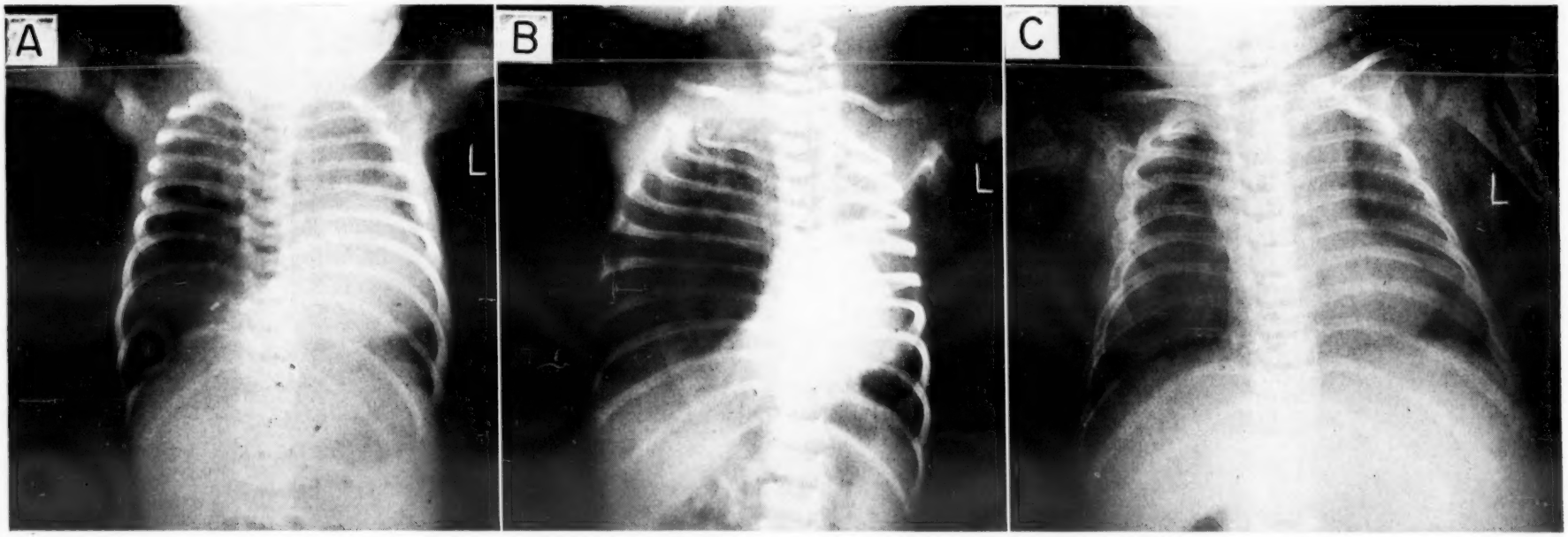

Fig. 7 (Case 4).—Roentgenograms of the chest *A*, at time of admission, *B*, twenty-four hours after admission, and *C*, postoperatively after resection of the emphysematous right middle lobe. The rapid progression of the emphysema and the restoration to normal by resection are demonstrated.

the operative impression of diffuse pulmonary emphysema. There was no evidence of an endobronchial obstructive process or aberrant vessels. Microscopically the lung revealed marked diffuse alveolar emphysema and patchy areas of atelectasis and unexpanded lung.

We have seen one other child recently who had a history similar to that of the previous patient. The findings were less severe. Similarly, a left exploratory thoracotomy was carried out at one year of age under the impression that we were probably dealing with tracheal compression due to an aberrant vessel. Here again only diffuse emphysema was encountered. There was no evidence of a congenital anomaly producing tracheal or bronchial compression. This child is still alive but continues to have severe respiratory difficulties and intermittent episodes of cyanosis. This situation may represent a less severe form of traumatic emphysema compatible with life.

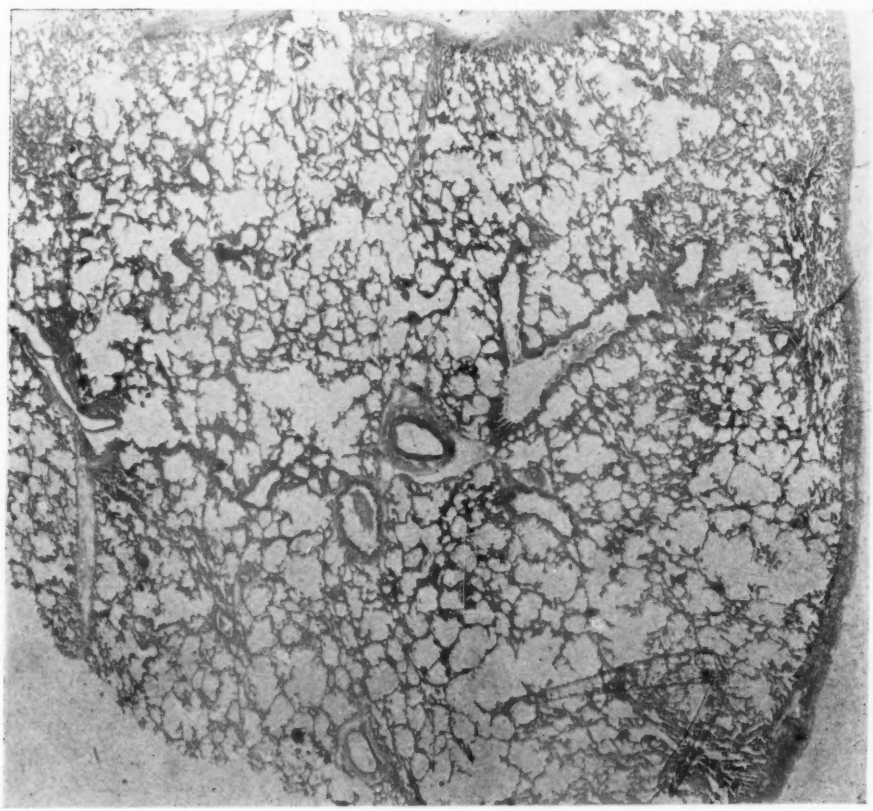

Fig. 8 (Case 4).—Photomicrograph showing extreme pulmonary emphysema with fragmentation of alveolar septa.

Comment.—The observation of interstitial or alveolar emphysema is not an uncommon finding in newborn infants in the autopsy room. These findings are mostly of a generalized character, but some atelectatic parenchyma and unexpanded lung remain interspersed between the emphysematous areas. Overactive insufflation of oxygen and forceful resuscitative measures of one kind or another usually play a determining role in the development of those findings. Undoubtedly permanent progressive damage can result after the initial production of the traumatic emphysema, breakdown of alveolar walls, and fragmentation of pulmonary parenchyma. Whether this mechanism is also responsible for the more localized forms of lobar or segmental emphysematous changes is not definite but certainly is a possibility.

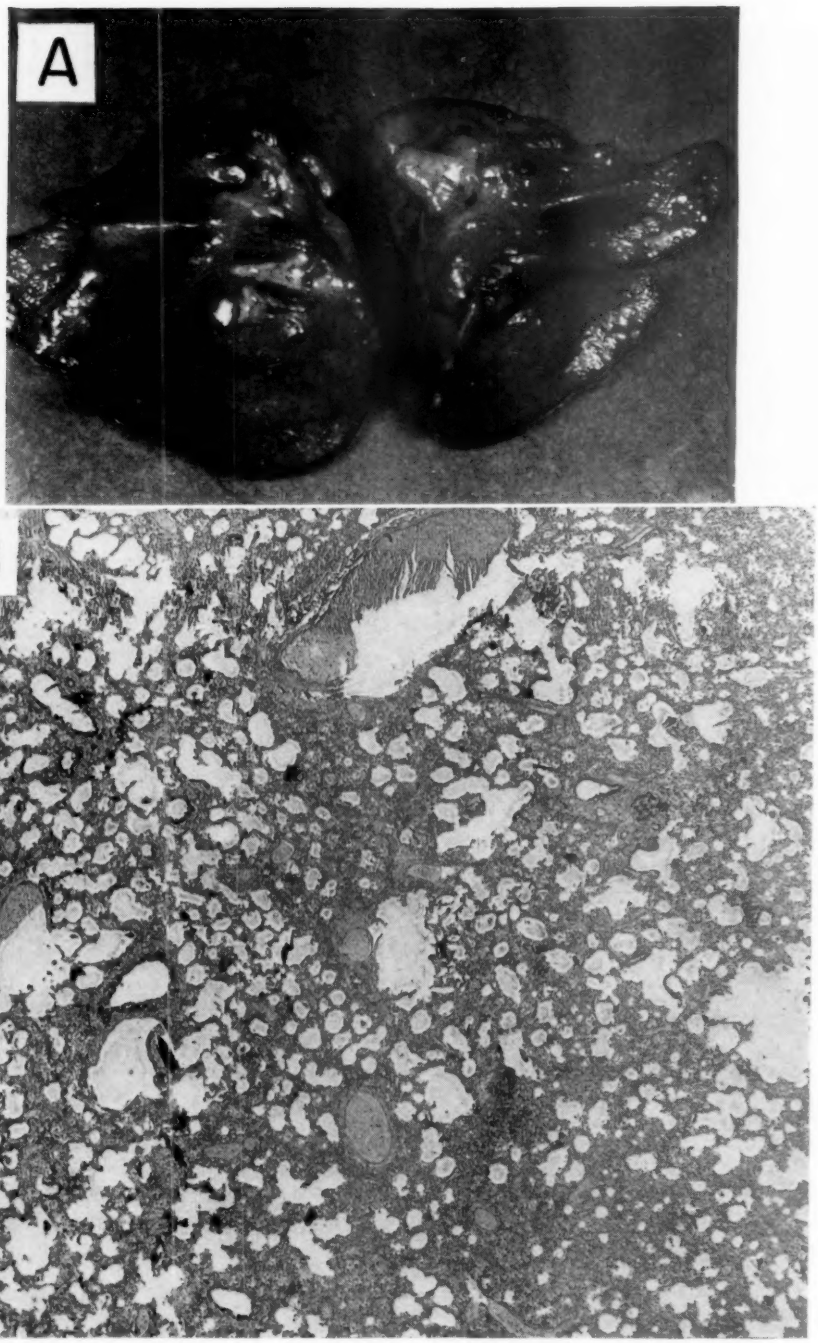

Fig. 9 (Case 5).—Photograph (*A*) and photomicrograph (*B*) of the lung removed at post mortem examination. The emphysematous areas are visible along the margins of the gross specimen and in the photomicrograph.

DIAGNOSIS

The awareness of a surgically remediable lesion in an infant with severe progressive respiratory difficulty is considered by the authors the most important aspect. The history of progressive respiratory difficulty beginning at or shortly after birth has been uniformly observed by us. The physical findings of a severely emphysematous type of chest cage, limited costal excursions during the respiratory efforts, intermittent cyanosis, tracheal shift, and unilateral hyperresonance with diminution of breath sounds over the same area are nearly always present. Roentgenographic findings of the chest in patients with localized emphysematous involvement demonstrate the marked and often rapidly

Fig. 10 (Case 6).—Photomicrograph showing marked interstitial emphysema, atelectasis, and unexpanded infantile lung.

progressive area of emphysema producing displacement of the normal surrounding structures and mediastinum. Atelectasis of the adjacent as well as of the contralateral lung and depression of the ipsilateral hemidiaphragm will be evident. In all our patients lung herniations through the anterior mediastinum were observed.

In patients presenting generalized pulmonary emphysema, lesions producing tracheal obstruction such as aortic rings and aberrant subclavian vessels should

be ruled out by means of bronchoscopy, Lipiodol esophagrams, and occasionally by angiocardiography.

TREATMENT

It is our belief that the only acceptable treatment of localized progressive emphysema is resection of the involved pulmonary tissue. In many instances this represents an emergent procedure which should be carried out as soon as the diagnosis has been established. The condition of those infants improves rapidly as soon as the thoracic cage has been opened. The increased intrapleural pressure is relieved immediately and the atelectatic lung parenchyma is permitted to expand. Partial obstruction of the venous return to the heart is relieved. This combined with expansion of the atelectatic lung alleviates the often pronounced cyanosis. The period of time between intratracheal intubation for anesthesia purposes and opening of the pleural space is a critical one. The emphysema progresses rapidly under positive pressure oxygen insufflation. In patients with apparently generalized pulmonary emphysema, exploration has occasionally been carried out if the previously mentioned studies were suggestive of compressive extratracheal lesions. This latter situation has been encountered rather infrequently.

SUMMARY

Attention is directed to the existence of a form of localized and progressive pulmonary emphysema in infants. This lesion may be caused by congenital cystic disease, localized bronchial abnormalities, or obstruction. Occasionally, it may be due to traumatic emphysema produced by overly energetic resuscitative measures. Early recognition and prompt surgical treatment frequently will be followed by a successful outcome. Exemplary cases are included.

Patients are presented to support the concept that overly vigorous resuscitative measures in the newborn may result in a generalized type of pulmonary emphysema. Surgical exploration is occasionally indicated in this group of patients if diagnostic studies suggest the presence of tracheal compression by extrinsic lesions.

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DISCUSSION

DR. RAVITCH (New York, N. Y.).—As the infant mortality rate from various other causes drops lower and lower, we begin to find new causes for infant mortality, which, as in the cases presented by Dr. Ehrenhaft, are sometimes the result of over-vigorous attempts at preserving ill children. One of the things that occurs to one is to wonder about the mental status some time later of the children who survived. All of these children, with the exception of the first who had congenital cystic disease, appeared to have started out with atelectasis, and it is well known, even without vigorous attempts from the outside to assist respirations, that these children in the course of strong respiratory efforts may develop emphysema and even pneumothorax, on their own. We have seen a number of patients in whom once pneumothorax developed, very prompt intervention with the insertion of an intercostal tube and negative suction has permitted the lung to expand. It is a brillant piece of work to have picked up some of these patients with localized lesions in whom a lobectomy or segmental resection was able to achieve a cure.

EXPERIMENTAL TUBERCULOSIS

IV. Effects of Occlusion of Pulmonary Veins on Tuberculosis in Monkeys

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(From the Departments of Surgery of the Vanderbilt University School of Medicine, the St. Louis University School of Medicine, and the Laboratory of Infectious Diseases of the National Institutes of Health)

IN PREVIOUS reports[1-3] we have described the effects of "arterialization" of the lung by anastomosis between systemic and pulmonary arteries and by ligation of pulmonary arteries in monkeys with induced tuberculosis. As a further phase in a systematic investigation of experimental alteration of the circulation in pulmonary tuberculosis, this report is concerned with the effects of occlusion of pulmonary veins on induced tuberculosis in monkeys.

METHODS

In these experiments 73 healthy Macaca mulatta monkeys were used. All were selected from carefully segregated stock animals which had shown consistently negative reactions to repeated tuberculin tests. All monkeys were submitted to thoracotomy. In 9 animals the superior pulmonary vein on the left or right was divided and ligated. In 56 monkeys an effort was made to produce gradual occlusion of the superior and inferior pulmonary veins on the left by the application of encircling bands of various fibrogenic materials. Simple thoracotomy was performed as a control in the remaining 8 animals.

The standard dose of the same virulent human strain of tubercle bacilli which was used in the previously reported experiments[1-3] was given intravenously (saphenous vein) to each monkey. Approximately one-half of the animals were given the infecting dose of organisms one to three days before operation, and the remainder received the infecting dose six to forty-eight days after operation.

BACTERIOLOGIC TECHNIQUE

A virulent strain of *Mycobacterium tuberculosis* isolated by one of us (B. J. O.) at the National Institutes of Health was used in these experiments. The virulence of the strain, the details of culture, and the standardized technique employed in preparation of emulsions for animal inoculation have been discussed in a previous communication.[1] The dose of tubercle bacilli given intravenously to each monkey in the present experiments consisted of 1 c.c. of a suspension containing 10^{-4} mg. of organisms per cubic centimeter.

Read at the meeting of the Society of University Surgeons, St. Louis, Mo., Feb. 12-14, 1953.

OPERATIVE TECHNIQUE

Intravenous pentobarbital sodium anesthesia (30 mg. per kilogram) with morphine-atropine premedication was used. Pulmonary ventilation was maintained by means of a mechanical respirator which delivered oxygen through an endotracheal tube. Aseptic surgical technique was used in all operations.

The chest was entered anteriorly through the fourth or fifth intercostal space on the left or right. In a few monkeys the superior pulmonary vein was dissected free, doubly ligated, and divided. In a large group of monkeys the superior and inferior pulmonary veins were dissected free extrapericardially and were banded with strips of a fibrogenic plastic material as in Fig. 1. In some of these animals polythene was used, in others nylon treated with x-ray film emulsion* was applied, and in the remaining monkeys the bands consisted

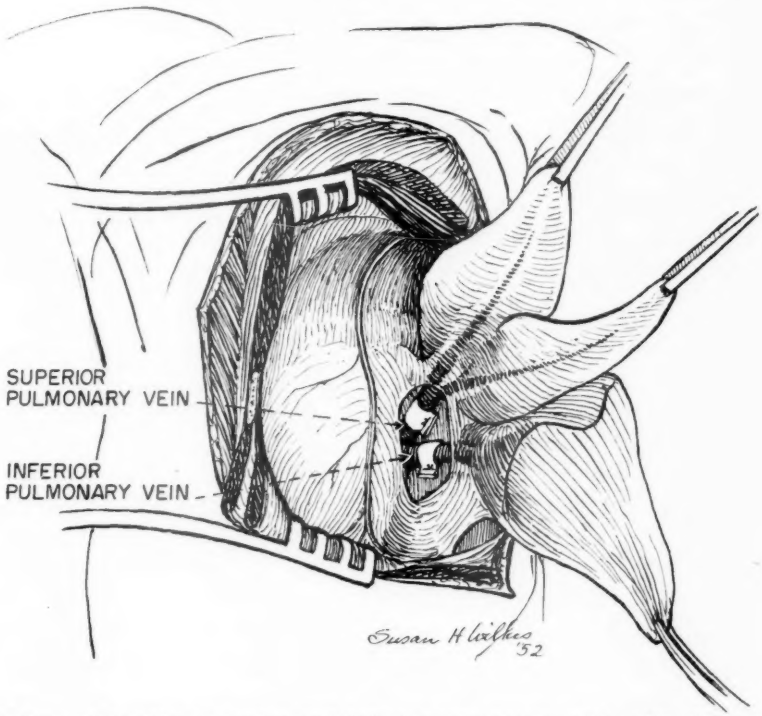


Fig. 1.—Technique of banding superior and inferior pulmonary veins with strips of fibrogenic plastic material.

of polythene coated with dicetyl phosphate.† The plastic bands were approximately 6 to 8 mm. in width and were snugly applied circumferentially to the veins so as to produce slight constriction. After the venous ligation or banding, the lung was carefully reinflated and closure of the chest wall was carried out with interrupted fine silk sutures.

In control thoracotomy the chest was entered in the fourth intercostal space on the right or left; the veins were not disturbed. In these cases the

*Prepared at the suggestion of Dr. Mark Kai-Hsi Wang by immersing thin nylon cloth in a solution of cleared radiographic film in acetone.

†Prepared at the suggestion of Dr. Charles Hufnagel by treating Du Pont's polythene film with a saturated solution of dicetyl phosphate in toluene. At least four coats of dicetyl phosphate were applied to each strip of film used.

lung was packed down with moist gauze for a few minutes, after which it was carefully reinflated and closure of the chest wall was carried out. Following operation each monkey received a single intramuscular injection of 300,000 units of penicillin in oil. The animals were kept in individual cages and were fed stock diet until death.

RESULTS

Of the 73 monkeys submitted to thoracotomy there were ten early postoperative deaths. Nine of these animals died of hemorrhagic pulmonary congestion within one to twelve days after the venous occlusion; in 1 monkey death was due to faulty anesthesia. Another animal died forty days after operation with pulmonary consolidation before receiving the infecting dose of organisms.

Tuberculosis developed and progressed to a fatal termination in the 62 remaining monkeys. A complete autopsy was performed immediately after death in each case. A special attempt was made to compare the character and extent of the tuberculous process in the lung or the lobes on the side of the venous occlusion with the lesions of the other pulmonary units of the same animal and with the lesions in the lungs of the control animals. Careful dissection, probing, and in many instances injection of pulmonary veins were carried out to determine the degree of venous occlusion. To obviate prejudice in determining the effect of venous occlusion, independent assessment of the severity of the tuberculosis was made without knowledge of the degree of venous occlusion. Sections were taken from the lungs and other viscera for microscopic study. Color photographs were made as an aid in recording gross pathologic appearances.

LIGATION OF SUPERIOR PULMONARY VEIN

In 9 monkeys ligation and division of the superior pulmonary vein on the left or right was carried out. Four of these animals died with hemorrhagic congestion of the affected lobe in eight to twelve days. The 5 remaining animals were infected with the standard dose (10^{-4} mg.) of tubercle bacilli by intravenous injection. Three of these animals were injected with tubercle bacilli six to thirteen days after operation, and the other 2 received the infecting dose of organisms eighteen hours before operation. The 5 animals lived from 89 to 306 days after inoculation. Pertinent data for these animals are summarized in Table I.

TABLE I. EFFECTS ON TUBERCULOSIS OF LIGATION OF SUPERIOR PULMONARY VEIN

MONKEY	TIME OF INFECTION	SURVIVAL TIME (DAYS AFTER INFECTION)	EXTENT OF DISEASE IN LOBE WITH OCCLUDED VEIN IN COMPARISON WITH CONTROLS		
			MORE	LESS	NO DIFFERENCE
D-1	Preop.	306	+		
E-9	Preop.	113		+	
H-18	P.O.	89			+
H-40	P.O.	188			+
H-41	P.O.	124			+

Each of the 5 monkeys showed extensive tuberculosis at autopsy. In 3 of the monkeys there was no difference between the character or extent of the tuberculous process in the upper lobe* with interrupted venous drainage and the disease elsewhere in the lungs. In 1 animal the disease was somewhat less extensive in the affected upper lobe, and in the remaining monkey the upper lobe with altered circulation was the site of a more extensive caseous process than was found elsewhere in the lungs. Dense vascular adhesions bound the affected upper lobe to the chest wall in each of the 5 animals.

Extrapulmonary lesions in these monkeys were concentrated in liver, lymph nodes, and spleen. Microscopic study of sections from the lungs and other viscera demonstrated numerous tubercle bacilli and confirmed the gross findings.

ATTEMPTS TO PRODUCE GRADUAL OCCLUSION OF SUPERIOR AND INFERIOR PULMONARY VEINS, LEFT, WITH "REACTIVE" POLYTHENE

In 18 monkeys the superior and inferior pulmonary veins on the left were snugly banded with strips of supposedly "reactive" polythene. The standard dose (10^{-4} mg.) of tubercle bacilli was given intravenously to 13 of these animals eighteen to twenty-four hours before operation and to 5 other monkeys twenty-six days after operation. The animals lived from 70 to 165 days after inoculation. Pertinent data for these monkeys are summarized in Table II.

TABLE II. EFFECTS ON TUBERCULOSIS OF ATTEMPTS TO PRODUCE GRADUAL OCCLUSION OF PULMONARY VEINS OF LEFT LUNG WITH POLYTHENE

MONKEY	TIME OF INFECTION	SURVIVAL TIME (DAYS AFTER INFECTION)	ESTIMATE OF DEGREE OF OCCLUSION OF PULMONARY VEIN		EXTENT OF DISEASE IN LOBE WITH OCCLUDED VEIN IN COMPARISON WITH CONTROLS					
					UPPER LOBE			LOWER LOBE		
			SUPERIOR (%)	INFERIOR (%)	MORE	LESS	NO DIFFERENCE	MORE	LESS	NO DIFFERENCE
CA-601	P.O.	102	0	0			+	+		
CA-591	P.O.	106	100	90		+			+	
CA-651	P.O.	101	50	100		+			+	
CA-581	P.O.	153	90	50		+				+
CA-561	P.O.	104	0	0		+			+	
CA-571	Preop.	158	40	40	+			+		
CA-611	Preop.	70	0	0			+			+
CA-521	Preop.	99	0	20	+			+		
CA-641	Preop.	87	40	0			+			+
CA-11	Preop.	107	0	0			+			+
CA-481	Preop.	120	0	0			+			+
CA-531	Preop.	137	100	20		+				+
CA-551	Preop.	119	20	0			+			+
CA-10	Preop.	79	20	0			+			+
CA-541	Preop.	131	100	100	+			+		
CA-511	Preop.	101	20	0			+			+
CA-491	Preop.	99	0	0			+			+
CA-621	Preop.	165	80	80			+			+

Extensive tuberculosis was found at autopsy in each monkey. Of the thirty-six veins which had been banded with polythene in this group of 18 monkeys,

*For the sake of simplicity in presenting these data the left middle lobe, which is well defined in most monkeys, is considered to be a part of the upper lobe since its vein is usually a tributary of the superior pulmonary vein.

twenty-five showed little or no evidence of constriction (less than 50 per cent). In the twenty-five lobes drained by these minimally constricted veins, the extent and character of the tuberculous process was not significantly altered: the disease in eighteen of these lobes was similar to that in the opposite lung of the same animals and in both lungs of control animals; in five lobes the disease was somewhat more extensive and in two lobes somewhat less extensive than elsewhere in the lungs.

Eleven veins showed a degree of occlusion at autopsy which ranged from 50 per cent to 100 per cent. In the eleven lobes drained by these veins the disease was unaltered in three, it was somewhat more extensive in two, and in six there was distinctly less disease than in the opposite lung of the same animal or in both lungs of control animals. Examples of these differences in the disease process are seen in Fig. 2.

A. *B.*

Fig. 2.—Photographs of fixed lungs (dorsal view) of 2 monkeys which died with tuberculosis after banding pulmonary veins on left with polythene. *A*, CA-531 at autopsy showed 100 per cent occlusion of superior vein but only 20 per cent occlusion of inferior vein. Note minimal disease in left upper lobe. *B*, CA-651 at autopsy showed 50 per cent occlusion of superior vein and 100 per cent occlusion of inferior vein. Note minimal disease in entire left lung.

Extrapulmonary lesions in these animals were concentrated in liver, spleen, and lymph nodes. Microscopic studies confirmed the gross findings.

ATTEMPTS TO PRODUCE GRADUAL OCCLUSION OF SUPERIOR AND INFERIOR PULMONARY VEINS, LEFT, WITH NYLON

In 14 monkeys the superior and inferior pulmonary veins on the left were banded with strips of nylon cloth treated with x-ray film emulsion. Four of these animals died postoperatively with hemorrhagic congestion of the left lung before injection with tubercle bacilli. The 10 remaining animals were given the

standard dose (10^{-4} mg.) of organisms by intravenous injection thirty-three to forty-eight days after operation. The monkeys lived from 73 to 225 days after inoculation. Pertinent data for these animals are summarized in Table III.

TABLE III. EFFECTS ON TUBERCULOSIS OF ATTEMPTS TO PRODUCE GRADUAL OCCLUSION OF PULMONARY VEINS OF LEFT LUNG WITH NYLON

MONKEY	TIME OF INFECTION	SURVIVAL TIME (DAYS AFTER INFECTION)	ESTIMATE OF DEGREE OF OCCLUSION OF PULMONARY VEIN		EXTENT OF DISEASE IN LOBE WITH OCCLUDED VEIN IN COMPARISON WITH CONTROLS					
					UPPER LOBE			LOWER LOBE		
			SUPERIOR (%)	INFERIOR (%)	MORE	LESS	NO DIFFERENCE	MORE	LESS	NO DIFFERENCE
H-51	P.O.	198	0	0			+			+
H-52	P.O.	73	0	0			+			+
H-53	P.O.	225	40	0		+				+
H-54	P.O.	123	40	0		+			+	
H-57	P.O.	99	50	50		+			+	
H-59	P.O.	85	0	0	+					+
H-61	P.O.	106	90	80		+			+	
H-62	P.O.	74	0	0			+			+
H-63	P.O.	95	100	0			+			+
H-65	P.O.	155	0	0			+			+

Extensive tuberculosis was found at autopsy in each monkey. Fifteen of the twenty veins which had been banded in this group of 10 animals showed little or no evidence of constriction (less than 50 per cent). In the fifteen lobes drained by these minimally constricted veins there was no evidence of any consistent alteration of the extent or character of the tuberculous process; in eleven of these lobes the disease was similar to that found elsewhere in the lungs of the same monkey and in the lungs of control monkeys; in one lobe the disease was somewhat more extensive and in three lobes slightly less extensive than elsewhere in the lungs.

The five other veins showed at autopsy greater degrees of occlusion (50 to 100 per cent). Among the corresponding five lobes there was less extensive tuberculosis in four than was found elsewhere in the lungs, and in one lobe the tuberculous process remained unaltered. Examples of the differences in the tuberculous process in the lungs of these animals are seen in Fig. 3.

Extrapulmonary lesions in these animals were similar in character and distribution to those previously described. Microscopic study of sections from the lungs and other viscera substantiated the gross findings.

ATTEMPTS TO PRODUCE GRADUAL OCCLUSION OF SUPERIOR AND INEFRIOR PULMONARY VEINS, LEFT, WITH POLYTHENE COATED WITH DICETYL PHOSPHATE

In 24 monkeys the superior and inferior pulmonary veins on the left were firmly banded with strips of polythene coated with dicetyl phosphate. Three of the animals died in the early postoperative period: in two instances death was associated with hemorrhagic pulmonary congestion and in one. with faulty anesthesia. The 21 remaining monkeys were given the standard dose (10^{-4} mg.) of tubercle bacilli by intravenous injection. Ten of these animals received the

infecting dose of organisms three days before operation and 11 others were infected twenty-two to thirty days after operation. The 21 animals lived from 71 to 214 days after inoculation. Pertinent data for these monkeys are summarized in Table IV.

TABLE IV. EFFECTS ON TUBERCULOSIS OF ATTEMPTS TO PRODUCE GRADUAL OCCLUSION OF PULMONARY VEINS OF LEFT LUNG WITH POLYTHENE COATED WITH DICETYL PHOSPHATE

MONKEY	TIME OF INFECTION	SURVIVAL TIME (DAYS AFTER INFECTION)	ESTIMATE OF DEGREE OF OCCLUSION OF PULMONARY VEIN		EXTENT OF DISEASE IN LOBE WITH OCCLUDED VEIN IN COMPARISON WITH CONTROLS					
					UPPER LOBE			LOWER LOBE		
			SUPERIOR (%)	INFERIOR (%)	MORE	LESS	NO DIFFERENCE	MORE	LESS	NO DIFFERENCE
H-98	P.O.	85	0	0			+			+
H-99	P.O.	80	100	100		+			+	
H-100	P.O.	88	40	40			+	+		
H-102	P.O.	160	100	100		+			+	
H-103	P.O.	96	60	0		+			+	
H-104	P.O.	161	100	0			+			+
H-105	P.O.	97	20	100			+			+
H-107	P.O.	192	0	100			+			+
H-108	P.O.	117	60	60			+			+
H-109	P.O.	80	100	0		+				+
H-110	P.O.	214	80	100		+				+
H-112	Preop.	201	60	60		+			+	
H-113	Preop.	127	60	60			+			+
CAH-54	Preop.	77	100	100		+			+	
CAH-55	Preop.	84	100	20	+					+
CAH-56	Preop.	110	80	100		+			+	
CAH-57	Preop.	187	80	60			+			+
CAH-58	Preop.	73	60	100			+			+
CAH-59	Preop.	100	20	20			+			+
CAH-63	Preop.	99	100	0			+			+
CAH-66	Preop.	71	100	0			+			+

Extensive tuberculosis was found at autopsy in each of these 21 monkeys. Of the forty-two veins which had been banded at operation, fourteen showed little or no evidence of constriction (less than 50 per cent). In the fourteen lobes drained by these minimally constricted veins there was no significant alteration of the tuberculous process: in twelve of the lobes the lesions were similar to those elsewhere in the opposite lung of the same monkey and in the lungs of control animals; in one lobe the disease was more extensive and in one other, slightly less extensive than elsewhere in the lungs.

The twenty-eight remaining veins showed at autopsy greater degrees of occlusion (50 to 100 per cent). In the corresponding lobes the tuberculous process was unaltered in thirteen, it was somewhat more extensive in one, and in fourteen lobes there was distinctly less disease than in the opposite lung of the same animal or in both lungs of control monkeys. Examples of these differences in the disease process are seen in Fig. 4.

Extrapulmonary lesions in this group of monkeys were concentrated in liver, spleen, and lymph nodes and were generally similar in distribution to those of the other groups. Microscopic studies confirmed the gross observations.

CONTROL THORACOTOMY

In 8 monkeys simple thoracotomy was performed as a control. The standard dose (10^{-4} mg.) of tubercle bacilli was given intravenously to 4 of these

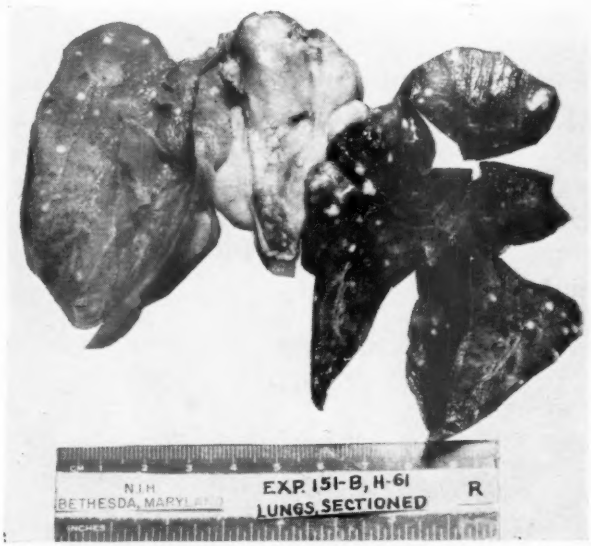
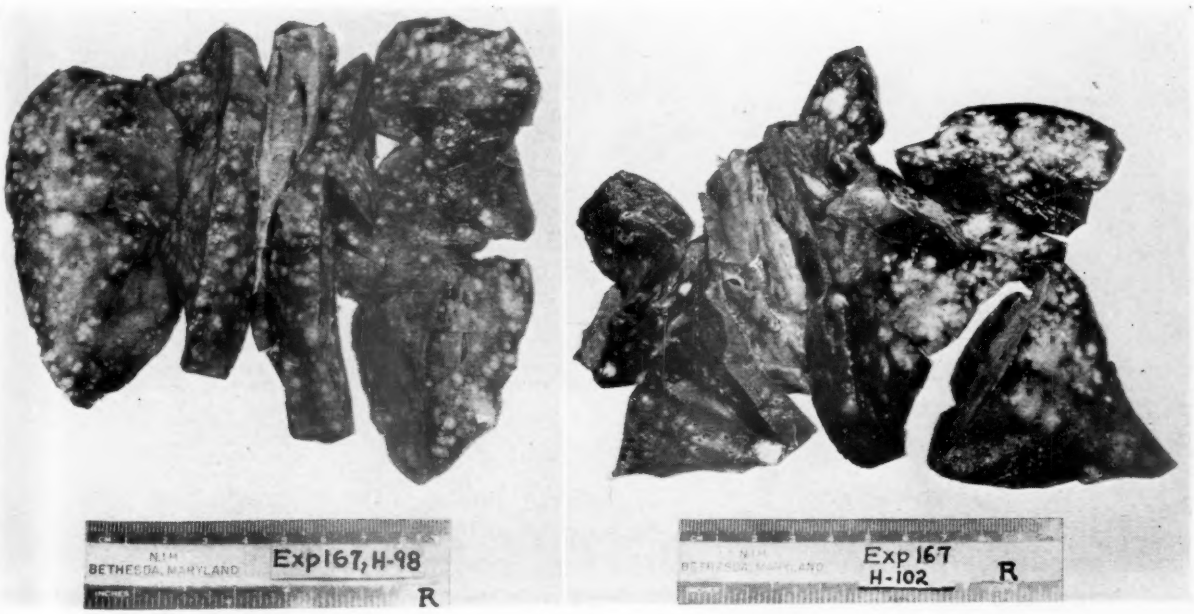


Fig. 3.—Photograph of fixed lungs (dorsal view) of monkey H-61 which died with tuberculosis after banding pulmonary veins on left with nylon. At autopsy there was almost complete occlusion of superior and inferior veins on left and less extensive disease in left lung than in right.



A. *B.*

Fig. 4.—Photographs of fixed lungs of 2 monkeys which died with tuberculosis after banding pulmonary veins on left with polythene coated with dicetyl phosphate. *A*, H-98 at autopsy showed no evidence of occlusion of left pulmonary veins and no difference in distribution of tuberculous lesions in the two lungs. *B*, H-102 at autopsy showed 100 per cent occlusion of both pulmonary veins on left. Note minimal disease in left lung.

animals eighteen to twenty-four hours before operation and the other 4 received the infecting dose of organisms six to twenty-one days after operation. The monkeys lived from 76 to 280 days after inoculation.

At autopsy in each of these 8 animals the lungs showed an equal distribution of tubercles of miliary type, ranging from 1 to 5 mm. in diameter. There were no observable differences between the lung on the side of thoracotomy and the opposite lung from the standpoint of character or extent of the disease process. Typical findings at autopsy in the lungs of these animals are illustrated in Fig. 5.

Extrapulmonary lesions in these control animals were similar in character and distribution to those in the monkeys which were submitted to the various pulmonary vein procedures. Microscopic study of sections from the lesions confirmed the gross findings.

Fig. 5.—Photograph of fixed lungs (dorsal view) of monkey which died with tuberculosis after simple thoracotomy, right, as control. Note equal distribution of tuberculous lesions in the two lungs.

DISCUSSION

These experiments indicate that one may influence the progress of induced tuberculosis in a lobe of the monkey's lung by occlusion of the pulmonary venous drainage. When the venous occlusion was abrupt, as in the animals with ligation and division of a lobar vein, there was a high incidence of fatal hemorrhagic congestion. In those animals which survived this division of the veins, the lungs showed no consistent alteration of the tuberculous process.

Attempts to produce gradual occlusion of pulmonary veins resulted in many failures; this was due in part to improper selection of fibrogenic materials. However, at autopsy a total of forty-four veins showed a degree of occlusion

varying from 50 to 100 per cent (Table V). Of the forty-four lobes drained by these constricted veins, twenty-four lobes (55 per cent) presented evidence of inhibition of the tuberculous process.* The inhibition of the tuberculous process in these twenty-four lobes was never absolute, rather, there was a quantitative reduction in the number and size of tubercles as compared to those in the opposite lung of the same monkey and in both lungs of the control animals.

TABLE V. SUMMARY OF DATA TO SHOW RELATION OF DEGREE OF CONSTRICTION OF PULMONARY VEIN TO CHANGES IN THE TUBERCULOUS PROCESS

METHOD OF PRODUCING CONSTRICTION	EXTENT OF DISEASE								TOTAL EXPERIMENTS
	LESS THAN 50% CONSTRICTION				MORE THAN 50% CONSTRICTION				
	LESS	NO DIFFERENCE	MORE	TOTAL	LESS	NO DIFFERENCE	MORE	TOTAL	
Polythene—dicetyl phosphate	1	12	1	14	14	13	1	28	42
Polythene (alone)	2	18	5	25	6	3	2	11	36
Nylon	3	11	1	15	4	1	0	5	20
Total	6	41	7	54	24	17	3	44	98

In these experiments, the production of gradual occlusion of pulmonary veins was designed to promote chronic passive congestion of the lung without inducing fatal hemorrhagic changes. The lobes which were found at autopsy to have significantly constricted veins were usually hyperemic and in most cases bound to the parietal pleura by vascular adhesions. The pathologic changes in pulmonary venous congestion have been detailed by Wyatt and others.[4] The hemodynamics of such congestion are under investigation.[5]

Montenegro,[6] Rokitansky,[7] Otto,[8] White,[9] and others have supported the concept that pulmonary tuberculosis is quite uncommon in individuals with mitral stenosis and other conditions associated with chronic pulmonary venous congestion. Bishop and Babey,[10] Davis,[11] and others have questioned the validity of this concept.

In 1907, Walsh[12] attempted to study the problem experimentally in dogs, but technical operative difficulties defeated his purpose. In 1911, Tiegel[13] studied the effects of venous congestion in the lungs of dogs and rabbits with induced pulmonary tuberculosis. He found that the venous stasis produced by placing

*In a comparison of the distribution of tuberculosis in the lungs of a series of monkeys which died after intravenous inoculation with 10^{-4} mg. of the same virulent strain of bacilli, some degree of "biologic variation" is expected. In a previous control experiment[1] with 22 monkeys there were five instances in which differences in extent of disease between right and left lungs were noted; in the lungs of the 8 monkeys which were submitted to simple thoracotomy as a control in the present experiments no differences were found; combined these give 17 per cent changes in a control comparison. Among the fifty-four lobes of the present experimental animals whose veins showed less than 50 per cent constriction, a difference in the tuberculous process occurred in 13 cases (24 per cent), well balanced for more or less, so that these cases seem to be unaffected by the test procedure and may be considered as controls. There were forty-four lobes in the present experiments with venous constriction of 50 to 100 per cent; of these, twenty-four showed less extensive disease than control lobes. (The combination of all cases with greater than 50 per cent constriction into a single group is justified by the fact that, of the seventeen instances where 100 per cent constriction was achieved, nine lobes [53 per cent] showed less extensive tuberculosis, indicating that the group is homogenous.)

Testing by χ^2 reveals the rather obvious information that the proportion which shows differences in the greater than 50 per cent constriction group is significantly larger than this proportion in the less than 50 per cent constriction group (probability less than .001). In the greater than 50 per cent constriction group the ratio of less extensive disease to more extensive disease of 24:3 differs significantly from theoretical equality (probability less than .001).

constricting ligatures around the pulmonary veins effected some inhibition of the disease induced by intravenous inoculation.

More recently Hyndman, Landt, and Mathes[14] have studied the effects of ligation of pulmonary veins on induced tuberculosis in dogs. A suspension of human tubercle bacilli was injected by catheter into each main bronchus, and the veins on the left side were ligated several days later. They stated that "the manner in which equivalent lesions healed in the same dog differed notably in the congested and uncongested lungs." Study of their protocols, however, suggests that it was usually difficult to detect any gross difference between the two lungs. Moreover, they stated: "The only microscopic difference of any possible significance that could be detected in the congested and uncongested lungs is that in the former there seemed to be a greater tendency toward vascularization with no sharp transition between caseous and viable lung, and this was evident to a striking degree in only one animal."

Edel,[15] Kerschner,[16] and O'Shaughnessy[17] have reported on a small number of patients with pulmonary tuberculosis who have been treated by partial occlusion of pulmonary veins with apparent benefit in some instances. However, the technique has not been given wide clinical trial.

Our present experimental findings are in agreement with the concept, based on fragmentary evidence, that the development of pulmonary tuberculosis may be somewhat inhibited by venous congestion in the lungs.

The mechanism of this inhibition is unsettled, but certain facts merit mention. If congestion is severe enough to diminish blood flow appreciably, there may be increased utilization of blood oxygen, resulting in an oxygen-poor environment which impairs the growth of tubercle bacilli. Moreover, the edema itself diminishes the amount of oxygen available through ventilation. With diminished perfusion of the lung, the opportunity for reseeding with circulating bacilli is likewise diminished. Such a situation might be considered as the antithesis of the experimental preparation with total arterialization of one lung.[1-3]

Extensive clinical application of these studies seems unlikely for a number of reasons, not the least of which is the difficulty of securing the proper degree of occlusion. Too little obstruction produces no effect on the tuberculosis, whereas sudden total occlusion is attended by a high mortality under the conditions of these experiments. More intensive chemotherapy might permit survival of these animals with total venous occlusion to one lung, as was noted in similar studies on dogs.[18] However, preliminary work suggests that there is no true respiratory function in a lung which reaerates after such intense congestion.[18] Therefore, the procedure seems clinically inadvisable. The importance of further clarification of this point is obvious.

SUMMARY

We have investigated the effect of pulmonary venous occlusion on induced tuberculosis in 73 monkeys.

In 56 animals attempts were made to produce gradual occlusion of the entire pulmonary venous drainage from the left lung. A significant degree of

occlusion was achieved in forty-four lobes, of which twenty-four showed evidence of inhibition of the tuberculous process.

Acute total occlusion of pulmonary veins from one lobe was carried out in 9 monkeys without consistent effect on the progress of the tuberculosis in the 5 survivors. There were no consistent differences in the tuberculous process in 8 monkeys subjected to control thoracotomy.

The relation of these findings to previous studies is outlined and their clinical significance is briefly mentioned.

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COMBINED ADRENALECTOMY-SYMPATHECTOMY IN THE TREATMENT OF PATIENTS WITH ESSENTIAL HYPERTENSION

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THREE years ago at the Hospital of the University of Pennsylvania a study of the effects of radical resection of the adrenal glands in a group of patients with severe, intractable, essential hypertension was begun. Our experience with patients subjected to thoracolumbar sympathectomy alone, radical subtotal adrenalectomy alone, and radical-to-total adrenalectomy combined with various types of sympathectomy has led us to believe that nearly complete, or complete, adrenalectomy combined with a subdiaphragmatic sympathectomy is a very satisfactory type of therapy.

Investigators have long realized that the adrenal gland is involved in the interrelated group of mechanisms which influence and control blood pressure levels.[1-3] The knowledge that hypotension is an outstanding feature of Addison's disease and that severe hypertensive states are associated with hyperfunction of the gland stimulated surgeons to attempt adrenalectomy for hypertensive cardiovascular disease as early as 1914.[4] A few isolated reports of this type of operation prior to the report of Green, Nelson, Dodds, and Smalley in 1950[5] gave some favorable results but were without sufficient evidence to substantiate the opinions offered. Realizing that surgery of the sympathetic nerves alone was not a completely satisfactory form of treatment of essential hypertension, it was decided to study the effectiveness of combined sympathectomy and radical adrenalectomy.

In the past thirty-five months, 69 patients with severe arterial hypertension have had bilateral resections of the adrenal glands combined with bilateral sympathectomies of various types. They have been followed from one to thirty-five months. They were selected for operation because they failed to respond to other forms of therapy, because they had an unusual form of the disease, or because the disease was progressing rapidly.

Of the 69 patients operated upon, 29 were women and 40 were men. The symptomatology found preoperatively was characteristic of hypertensive patients with headache being the most common complaint. Twenty-eight had evidence

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of impending or frank heart failure. Fifteen had a history of angina of a mild or moderate degree. The average preoperative blood pressure in the supine position was 206/127 mm. Hg.

The 69 patients were grouped according to Smithwick's criteria,[6] and it was found that 18 were in Group II, 18 were in Group III, and 33 were in Group IV. It is interesting to note that 33 of the 69 patients were in Group IV, the group that Smithwick considers unsuitable for thoracolumbar sympathectomy (Table I).

TABLE I. CLASSIFICATION OF PATIENTS

SMITHWICK GROUP	NO. OF PATIENTS
I	0
II	18
III	18
IV	33

The distribution of age by decades was found to be 1 in the second decade, 5 in the third, 11 in the fourth, 38 in the fifth, and 14 in the sixth decade (Table II).

TABLE II. AGE BY DECADES

DECADE	NO. OF PATIENTS
I	0
II	1
III	5
IV	11
V	38
VI	14

Various types of operative procedures were performed on the 69 patients. Some of those in the first of the series had had one adrenal removed during the second stage thoracolumbar sympathectomy, and at a later date had subtotal removal of the remaining gland. One patient had had a Peet subdiaphragmatic sympathectomy before he was subjected to subtotal adrenalectomy. Four patients had a modified Adson-type sympathectomy on one side and a Smithwick type of thoracolumbar sympathectomy on the other, combined with subtotal resection of the adrenal glands.

The largest single group of patients had a removal of 95 to 98 per cent of the total adrenal tissue, combined with a subdiaphragmatic sympathectomy and

TABLE III. TYPES OF OPERATIVE PROCEDURES

TYPE OF PROCEDURE	NO. OF PATIENTS
Subtotal Adrenalectomy (95-98%)	
Smithwick	8
Peet	1
Smithwick and modified Adson	4
Modified Adson	43
Total Adrenalectomy	
Smithwick	2
Modified Adson	11

splanchnicectomy (Table III). It was found by experience that it was necessary to remove almost all of the adrenal tissue in order to obtain adequate reductions in blood pressures in most patients.

The operation was performed in two stages with at least seven days between procedures. A subtotal resection of one adrenal was performed at the first operation, and a total removal of the remaining gland at the second. The approach was through a lateral subcostal incision beneath the twelfth rib.[7] The peritoneum was reflected anteriorly and the gland exposed at the upper pole of the kidney by blunt dissection. The portion of the gland left in situ was a small remnant at the hilus where the adrenal vein leaves the gland. The sympathectomy consisted of a modified Adson sympathectomy and splanchnicectomy. The twelfth thoracic ganglion and first and second lumbar ganglia, and intervening sympathetic trunks were removed. The greater and lesser splanchnic nerves were interrupted by excising one-half to three-fourths of an inch of these nerves as they pierced the diaphragm. In several men in whom it seemed desirable to preserve sexual function, the first and second lumbar ganglia were not removed on one side.

Recently a few patients have had total adrenalectomy and sympathectomy. This procedure is being tried because it was the impression of several members of the group studying the residual adrenal function that the most satisfactory reduction in blood pressures occurred in those patients who seemed to have the least amount of functioning adrenal tissue as determined in the later postoperative periods by electrolyte balance studies and hormone assay methods.[8] With increasing experience, the problem of maintenance therapy in these patients is not difficult, and therefore we have not hesitated to perform complete bilateral adrenalectomies.

RESULTS

The operative mortality for these patients has been two deaths in 69, or 2.9 per cent. Since operation 9 others have died, making the over-all mortality 15.9 per cent. It is worthy of note that 9 of the 11 patients now dead were in Group IV of Smithwick's classification (Table IV).

TABLE IV. MORTALITY IN SMITHWICK GROUPS

GROUP	NO. OF DEATHS
I	0
II	0
III	2
IV	9*

*Two operative deaths.

Since the follow-up period is still too short to allow comparison of the survival rates of our patients with those receiving other types of therapy, the results of this operation have been evaluated in terms of blood pressure reduction and improvement in symptoms and signs (Table V).

Patients whose postoperative blood pressures were 140/90 ± 10 mm. Hg on lying and standing were considered to have excellent results. Those with pressures of 140/90 ± ten on standing only were considered to have satisfactory

TABLE V. CLINICAL EVALUATION OF RESULTS OF COMBINED ADRENALECTOMY AND SYMPATHECTOMY IN SURVIVING PATIENTS

RESULTS	NUMBER OF PATIENTS	PER CENT OF TOTAL
Excellent (blood pressure 140/90 ± 10, lying and standing)	21	30.4
Satisfactory (blood pressure 140/90 ± 10, standing only)	13	19
Improved (blood pressure elevated, improved symptoms and signs)	28	40.5
Poor (blood pressure elevated, symptoms and signs unchanged)	7	10

results. If the patient continued to run elevated pressures but had improvement in symptoms and/or signs, he was classified as improved. If there was no response in blood pressure, symptoms, or signs, the result was listed as poor. The results in 21 patients were classed as excellent, in 13 satisfactory, in 28 improved, and in 7 poor. Thus we see that 49 per cent of the patients had normal pressures, at least in the standing position, 40 per cent were improved in regard to symptoms and signs, and 10 per cent were not benefited by the operative procedure.

In Group II and III patients, more than 60 per cent had excellent or satisfactory results (Table VI). In Group II, 39 per cent were improved with no poor results. In Group III, 28 per cent were improved with 6 per cent poor results. In Group IV, 34 per cent were excellent or satisfactory, 48 per cent improved, and 18 per cent were poor results. It is significant that 82 per cent of the Group IV patients were benefited by the operation.

TABLE VI. EVALUATION OF IMPROVEMENT IN SMITHWICK GROUPS

SMITHWICK GROUP	EXCELLENT (PER CENT)	SATISFACTORY (PER CENT)	IMPROVED (PER CENT)	POOR (PER CENT)
I	0	0	0	0
II	39	22	39	0
III	44	22	28	6
IV	18	16	48	18

The average postoperative blood pressure in the supine position for all patients was 163/109 mm. Hg. This represented an average fall of 43 mm. in systolic pressure and 18 mm. in diastolic pressure.

The arrest and regression of vascular damage has been quite remarkable in some instances. For example, 28 patients have had definite improvement in retinopathy, 24 have shown a decreased heart size, and 16 have shown improvement in electrocardiographic tracings.

One of the most outstanding findings occurring postoperatively has been noted in those patients who had evidence of cardiac decompensation prior to operation. Of the 28 patients with impending or frank failure, 23 are living, and of these only 2 require digitalis. Only 1 of the 5 patients now dead died of heart failure, the other four deaths being from other causes.

Among the 7 patients with a definite history of angina, 4 have had coronary occlusions since operation, one of which was fatal. Eight patients suspected of having occasional mild angina before operation are all living and have had no

further pain suggestive of angina. We do not feel that patients with definite angina of a moderately severe degree have benefited significantly from the operation.

Although Clark, Crosley, and Barker[9] found some laboratory evidence of improvement in renal function, we have not been able to demonstrate improvement in renal function by the phenolsulfonphthalein and urea clearance tests in these patients. This fact, plus the observation that almost all of the patients who have died since the operative procedure have had marked impairment of renal function, as indicated by phenolsulfonphthalein excretion, blood urea nitrogen levels, and urea clearance studies, has led us to believe that severe renal damage is the most important contraindication to operation. It has been our experience that patients with a blood urea nitrogen of 20 mg. per cent or more, a phenolsulfonphthalein excretion of less than 20 per cent in fifteen minutes, or a urea clearance of less than 50 per cent average normal function are not desirable candidates for adrenal resection.

With the exception of advanced renal damage, we have been unable to realize any definite correlation between preoperative findings and the cause of deaths occurring since operation. Of the 9 patients whose deaths were non-operative, 3 have died in uremia, 3 have had coronary occlusions, 2 have died in congestive failure, and 1 was thought to have died in adrenal insufficiency.

It is true that all but two of the deaths occurred in Group IV patients, but the fact remains that a large number of these patients, who were previously considered unsuitable for sympathectomy alone, are now living and enjoying a more comfortable existence than they were before operation.

MAINTENANCE THERAPY

When these studies were first undertaken, it was hoped that it might be possible to remove enough adrenal tissue to effect an adequate reduction in blood pressure without producing a state of adrenal insufficiency or frank Addison's disease. This has been possible in a few cases, but there is a very narrow margin of separation of these two situations. The majority of patients having a favorable response in blood pressure require small daily doses of cortisone, desoxycorticosterone, and sodium chloride. A few patients require cortisone replacement therapy and still continue to have elevated pressures. In these cases we have reason to believe that advanced renal damage has been responsible for the failure of reduction in blood pressure.

No replacement therapy is used at the time of the first stage operation. At the time of the second stage total adrenalectomy, 50.0 mg. of cortisone have been given on the day of operation, 100 mg. on the first postoperative day, 75.0 mg. on the second and third days, 50.0 mg. on the fourth, and 37.5 mg. on the fifth. As soon as the patient is able to take oral medications, 2 mg. of desoxycorticosterone are started. At the time of discharge from the hospital, the patient receives cortisone 12.5 mg. three times daily, desoxycorticosterone 2.0 mg. daily, and sodium chloride 1.0 Gm. three times daily post cibum. At the end of one month the dosages are changed according to the needs of the patient. The

maintenance dose of cortisone in our patients is 25.0 to 37.5 mg. per day. If 2 to 5 per cent of one adrenal is not removed, desoxycorticosterone and extra sodium chloride may not be necessary.

The maintenance therapy of these patients is no longer a serious problem, and the management of totally adrenalectomized patients is rarely more difficult than the management of those who have some remaining adrenal function. There is no standard regimen for maintenance therapy after the immediate postoperative period. The need for replacement therapy is best determined by the subjective symptoms of weakness and fatigue which usually occur in advance of changes in blood chemistries. The average patient quickly learns his own need for more or less replacement therapy. With proper replacement therapy, it is frequently not possible to tell at a glance which of the patients in our hypertension clinic have had bilateral total adrenalectomy and which ones have had only thoracolumbar sympathectomy.

The need for close follow-up contact with these patients by a group entirely familiar with the patients and their backgrounds cannot be too highly emphasized. Infections or other acquired diseases can be a threat to the patient's life, and it is imperative that, when such conditions arise, the patients be in the hands of physicians who understand the problem of maintenance therapy.

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DISCUSSION

DR. RALPH F. BOWERS (Memphis, Tenn.).—Mr. Chairman, the work that Dr. Zintel and Dr. Mackie have presented is excellent and represents a step forward during the remaining days of surgical influence in the treatment of hypertension. However, there is no question in my mind that some of the comments about the ability of adrenalectomy to reduce blood pressure in human beings with hypertension are incorrect. The blood pressure will be reduced, as Dr. Mackie stated, if a small enough remnant of adrenal tissue is left. I do not quite understand how Dr. Zintel and Dr. Mackie know that they have removed 98 per cent of the gland. I am not that good. I do not know what kind of micrometer they employ, but I leave a piece about the size of the fingernail on the little finger.

We have performed bilateral subtotal adrenalectomies on 28 patients. All of them were of the Group IV type; many of them were "Group IV plus," or the ultradesperate type. Strangely enough, these are the cases the "internists" want us to treat surgically.

Six of the 28 patients died in the early postoperative period, and 2 died later, one at three months and another at seven months.

The pressure has been reduced to normal in all except 2 of the 20 survivals and these 2 were the patients who died later. Obviously, we trade conditions in the patient; we make him subject to a low-grade manageable hypo-adrenalism instead of fatal hypertension. Any of these patients can be made hypertensive if he is given large enough doses of cortisone or Doca. This can be done if a level is reached in the substitutive therapy where the patient is a little bit hypo-adrenal, but still not hypertensive.

I think we have obtained reduction of pressure in a higher percentage of patients than Dr. Zintel and Dr. Mackie have. The chart shows their best results in the Group IV patients and those are the only patients we adrenalectomize. I do not believe the operation can be termed a routine one because of the difficulties and dangers of the substitutive therapy. I will grant Dr. Mackie that it is possible, with gained experience, to give this substitutive therapy without great danger, but the patient cannot be too far away from a physician who well understands the treatment of Addison's disease. For instance, our second late death happened when the patient's physician was ill, and another physician, not well versed in handling Addison crises, could not successfully handle the hypo-adrenal state; the patient died of adrenal insufficiency. This case alone takes the procedure out of the routine class. Nevertheless, great benefit has been gained for these patients.

DR. KEITH S. GRIMSON (Durham, N. C.).—Dr. Mackie has presented important and interesting observations concerning adrenalectomy and subdiaphragmatic splanchnicectomy in the treatment of patients with hypertension. His studies and those of others have been following with a conservative attitude. This society knows that medical methods for treating malignant hypertension are becoming increasingly more effective. Since there is no good method for predicting which patient is otherwise hopeless or should be selected for such a physiologically drastic procedure we have not performed adrenalectomy for hypertension.

It is important that an accurate evaluation of the efficacy of this procedure be obtained. The operation has afforded excellent physiologic and endocrine observations in patients. In the field of cortical hyperfunction or hyperplasia it has been established that consistent changes occur only with total adrenalectomy, not with removal of one gland and most of the other. There seems to be no happy medium between removal of too little with no effect and too much with requirement for replacement therapy. From the physiologic point of view only total adrenalectomy will afford good evidence.

Splanchnicectomy has occasionally achieved marked improvement and reduction of blood pressure in Group IV hypertensive patients who have been treated during a malignant exacerbation of the disease. Accordingly, splanchnicectomy performed with adrenalectomy will make clinical evaluation difficult, especially if the adrenalectomy is subtotal.

Subdiaphragmatic splanchnicectomy, or any splanchnicectomy, is itself an incomplete or subtotal procedure. Studies have demonstrated that significant interruption of the vasopressor pathways occurs only when sympathectomy also includes the stellate ganglia and upper thoracic chain. One hundred seventy-two patients have had "total" sympathectomy, including the stellate ganglia as well as the splanchnic area, during the last thirteen years. Of these, 95 were treated five to ten years ago and 84.2 per cent are now living. Results of any form of surgical treatment for hypertension can be best evaluated only after long periods of follow-up observation. Those for adrenalectomy will be awaited with interest.

DR. MACKIE (Closing).—I would like to thank Dr. Bowers and Dr. Grimson for their comments on the paper and to say that it is difficult to know the exact amount of adrenal tissue that is left in situ. Our figures represent the combined estimates of three or four people present at the time of operation.

Some of the patients in the first of the series had subtotal adrenalectomy alone, with removal of less than 90 per cent of the total adrenal tissue. The results in these cases did not seem to be as satisfactory as did those later in the series where an estimated 95 to 98 per cent resection was performed.

OBSERVATIONS ON EXPERIMENTAL BILE PERITONITIS

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(From the Surgical Unit of the General Research Laboratory, Veterans Administration Medical Teaching Group Hospital)

THE clinical observation of several patients who survived the intraperitoneal extravasation of bile in amounts up to 6,000 c.c. led us to doubt that large amounts of bile in the peritoneal cavity cause, as others have concluded, an intense chemical peritonitis which becomes secondarily infected and almost invariably causes death.

Review of the literature reveals experiences similar to ours which have stimulated researches into this problem since 1755,[10] but despite this there remain many controversial issues and unanswered questions. Among these are: the relative danger of the escape of bile into the peritoneal cavity, the lethal dose, the role of infection, the effect of bile on the peritoneum and viscera, the effects of cholemia, and the cause of death.

The experimental conclusions which have been reached reflect great difference of opinion. Some of these conclusions are:

1. Sterile bile is well tolerated by the peritoneal cavity and is accompanied by no great danger (Noetzel, McWilliams, Orth, Sick and Fraenkel, Buchanan, and Couvoisier quoted by Mentzer[18] who reached the same conclusion clinically).

2. Bile in the peritoneal cavity is dangerous[21] and is attended by serious sequelae. Investigators who hold this opinion are in disagreement as to the cause of death, as follows:

(a) *Toxicity of bile salts:* Wangensteen[24] and Manson and Eginton[15] stated that death in experimental bile peritonitis is due to the toxic action of absorbed bile salts (cholemia). Others[7, 22] objected to this on the ground that the bile salt blood level in such animals has not been significantly elevated, and in their experience death is due to other causes such as infection, shock from fluid loss, etc.

Bile salts are the toxic components of bile. The cholate radical is the important factor, there being no difference in the toxicity of sodium glycocholate and sodium taurocholate (Horrall and Carlson,[13] Harkins and associates[7]).

(b) *Infection:* When bile causes tissue damage, a septic process is set up by multiplication of clostridial organisms already present locally in the tissues (Andrews and Rewbridge[1]). Rewbridge[23] stated that infectious organisms may traverse the bowel wall and enter the peritoneal cavity because of permeability changes caused by bile salts. Ziegler and Orr[25] contended that infection is not a contributing factor (anaerobic cultures were not made).

Read at the meeting of the Society of University Surgeons, St. Louis, Mo., Feb. 12-14, 1953.

*Instructor, Division of Surgery, University of Tennessee College of Medicine.

(c) *Shock from intraperitoneal fluid loss:* Several observers have presented evidence that shock from intraperitoneal fluid loss may be the cause of death in these cases.[7, 15, 19]

3. The lethal dose of sterile bile intraperitoneally is approximately 5 c.c. per kilogram of body weight according to Horrall,[12] Harkins and co-workers,[6-9] and Moon and Morgan.[19]

This experiment was originally designed to determine only the lethal dose of bile administered intraperitoneally, because our clinical observations did not coincide with experimental reports. However, dogs which received bile in amounts usually considered lethal survived. Consequently, it became necessary to employ larger amounts of bile than had been thought sufficient to produce death, and with this the hitherto unappreciated importance of infection was apparent, as most of our animals died of virulent gas bacillus peritonitis and visceral gas gangrene. Henceforth, bacteriologic and pathologic studies were carried out.

MATERIAL AND METHODS

"Bile peritonitis" was produced in 108 healthy adult mongrel dogs, weighing from 5.4 to 20.4 kilograms, by injecting pooled bile into the subhepatic space through a ventricular cannula, which was introduced via a small incision in the linea alba and a purse-string opening in the peritoneum. The dogs were anesthetized with intravenous Nembutal. Operations were carried out under aseptic conditions. Survivals were sacrificed from fourteen to twenty-one days postoperatively, except for eight which were sacrificed from two to twelve hours postinjection. Autopsies were performed on all dogs.

Aerobic and anaerobic cultures were made of the bile used at the time of injection and of the intraperitoneal fluid recovered at autopsy, except in the first fourteen cases. Care was taken both at injection and at autopsy to prevent contamination by touching abdominal musculature.

Bile was injected in amounts varying from 5 c.c. to 800 c.c. (total) and from 0.6 c.c. per kilogram of body weight to 69.4 c.c. per kilogram of body weight.

The use of extremely large quantities of bile demanded a method of collecting large amounts (2,000 to 3,000 c.c.) under sterile conditions. Several methods, including that of Markowitz,[16] were tried without success. The best method proved to be the maintenance of a battery of six to eight "bile factories." These were dogs in which the common duct had been ligated and cholecystostomy performed, after which the animals were immobilized in plaster of Paris casts to prevent wound infection and contamination of the collecting apparatus. In spite of this, the bile became infected at the source within three or four days, and only one-third of our injections were sterile.

Sterilization of the bile by methods used by other investigators (autoclaving, filtering, desiccating, extracting, freezing, etc.) was not thought proper because of the chance of changing the chemical composition and, in turn, the lethal and toxic qualities of the bile. Inasmuch as infected samples had shown *Clostridium capitovalis* and other penicillin-susceptible organisms,

and inasmuch as the addition of penicillin did not materially alter the bile salt content by chemical analysis, penicillin was added to the bile immediately prior to injection in the amount of 10,000 U. per cubic centimeter in order to maintain sterility. Utilizing this technique, 69 per cent sterile injections were obtained.

Penicillinized bile was prepared using two techniques: in the first technique, the low dilution of 1,000,000 U. of penicillin per cubic centimeter of sterile water was used; in the second, each 1,000,000 U. of penicillin was diluted with 10 c.c. of sterile water in order to observe the effect of the dilution factor.

Autoclaved bile was used in four cases in order that its action might be compared with the action of plain and penicillinized bile.

Quantitative determination of blood bile salt levels was made pre- and postoperatively in five animals employing a modification of the technique of Irvin and associates.[14]

Kymographic recordings of the pulse and blood pressure were made before, during, and for variable periods after injection in several instances.

RESULTS

Lethal Dose.—Extremely small amounts of bile were initially employed in the experiment without untoward effect. The dose was gradually increased and the animals were found to survive sterile bile in amounts usually considered lethal (5 c.c. per kilogram of body weight), although Blalock[2] reported three survivals in which 20, 21, and 37 c.c. per kilogram were administered, respectively. It became apparent at this point, and remained so throughout the rest of the study, that within certain limits the lethal dose depends on whether or not the bile is infected. For example, with sterile bile in amounts less than 20 c.c. of bile per kilogram of body weight the mortality was only 23 per cent as compared to 62 per cent when the bile was infected (Fig. 1). Death was observed with as little as 0.8 c.c. of infected bile per kilogram of body weight. When amounts greater than 20 c.c. per kilogram of body weight were used, the mortality rate increased to 68 per cent as compared to 88 per cent for infected bile. Thus infection becomes less important when large amounts are used since the animal dies before infection has time to play its role. Considering all cases, the mortality rate remains relatively constant at approximately 25 per cent (due to infected bile) until a dose of 15 c.c. of bile per kilogram of body weight is reached. The mortality rate then rises as the dose is increased, reaching 85 per cent when a dose of 40 c.c. per kilogram of body weight is administered; however, one animal survived a dose of 50 c.c. per kilogram. The lethal dose of sterile bile averaged 20 to 40 c.c. per kilogram of body weight. These figures are more in accord with clinical observations.[5, 11] It should be remembered that 50 c.c. per kilogram would be equivalent to 3,500 c.c. of bile in the average-sized man.

The lethal dose of sterile bile was affected by the dilution factor involved in one of our methods of penicillinizing bile to maintain sterility. The mortality rate was 41 per cent when the high dilution was used as compared to

75 per cent for the low dilution. This bears out the conviction that the immediate reaction of the peritoneum to bile is the outpouring of fluid which dilutes it, thereby diminishing its local effect on the peritoneum and viscera.

Cause of Death.—Death of animals following intraperitoneal bile injections assumed definite patterns. Animals dying from effects of bile peritonitis did so within twenty-four hours except in three instances, two at thirty-three and one at forty-five hours.

Cholemia: Animals dying within the first ten hours (several died within one or two hours) were those injected with large amounts of bile, sterile or infected. At autopsy no gross abnormalities were noted in sterile or infected cases. Kymographic recordings revealed bradycardia and extreme hypotension suggesting the absorption of toxic amounts of bile salts.[24] In five instances samples of blood were withdrawn when death seemed imminent, and bile salt determinations were made. The bile salt blood level was increased in all cases, averaging twenty-five times the preinjection levels (Table I).

TABLE I. RISE IN BILE SALT BLOOD LEVELS FOLLOWING INTRAPERITONEAL INJECTION OF BILE

DOG	AMOUNT OF BILE INJECTED (C.C. PER KG.)	PREINJECTION LEVEL (MG. %)	POSTINJECTION TIME INTERVAL (MIN.)	POSTINJECTION LEVEL (MG. %)	INCREASE (NO. OF TIMES PREINJECTION LEVEL)
688	46.5	0.29	150	21.0	71
698	47.8	1.09	5	17.0	16
701	69.4	0.28	300	0.9	3
703	58.4	0.16	300	4.5	29
708	38.9	0.35	300	1.4	4
Average		0.41		8.9	25

Intraperitoneal fluid loss: The accumulation of fluid intraperitoneally in amounts sufficient to cause death was observed in only 16 per cent of our animals, and would seem to be of minimal importance. Those showing significant increases died within fifteen to thirty hours after injection. Animals dying with generalized peritonitis had less fluid in the peritoneal cavity at death than the amount injected. Animals injected with bile treated with high dilutions of penicillin accumulated more fluid than those injected with low dilutions. The four animals injected with autoclaved bile (all died) revealed less fluid at autopsy than the amount injected.

Pathologic effect: Microscopic examination of the viscera in dogs dying in the early interval revealed minimal changes consisting primarily of cuboidalization of the serosal cells and congestion of the liver, spleen, kidneys, and lungs (Fig. 2). However, in a few cases necrosis of the capsules and adjacent parenchymal cells of the solid viscera was noted (Fig. 3).

A different picture was observed in animals dying between ten and twenty-four hours after injection depending on whether or not the bile was infected. The injection, in fourteen instances, of bile infected with a combination of gas bacilli *(Clostridium capitovalis)* and other pyogenic organisms proved to be the most lethal, the mortality rate being 100 per cent. However, no animal died less than sixteen hours after injection, although bile in amounts averaging 30 c.c. per

kilogram was used. Generalized peritonitis and/or necrosis of the liver, spleen, and pancreas were responsible for death in these animals. In the twenty-eight remaining animals injected with infected bile, peritonitis was grossly evident in only four and questionable in three. Hemorrhagic pancreatitis was present in two of these animals (Fig. 4). The average duration of life after injection was twenty-one hours.

Seven of the eighteen animals which died at the later interval following the injection of sterile bile revealed gross autopsy findings which consisted of mild peritonitis as evidenced by injection of serosal blood vessels. Hemorrhagic pancreatitis was present in two instances.

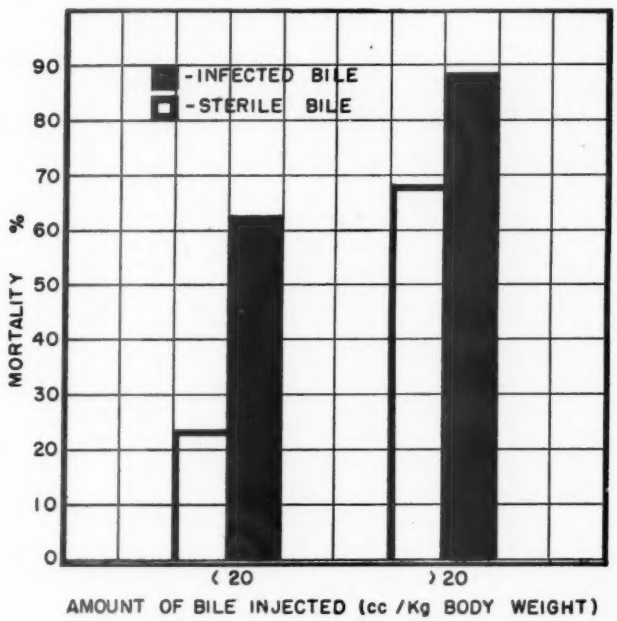


Fig. 1.—Graph demonstrating the relative importance of infected bile as compared to sterile bile in doses less than and greater than 20 c.c. per kilogram of body weight.

Astonishingly enough, microscopic examination of the viscera of animals dying at the later time interval following both sterile and infected bile injections showed these organs to have been seriously damaged. The capsules, visceral peritoneum, and adjacent parenchymal cells of the liver, spleen, and pancreas revealed extensive necrosis (Fig. 5). Less extensive serosal surface necrosis was observed in the duodenum and kidneys in only a few animals. Fat necrosis was present in many instances.

Andrews and co-workers[1] described the sequence of events in the development of bile peritonitis as including local tissue damage caused by bile salts which promote the multiplication of anaerobic organs already present within the tissues. Rewbridge[23] postulated that bacteria may pass through the wall of the intestine into the peritoneal cavity because of increased permeability due to bile salts. Certain of our observations substantiate this, inasmuch as the development of gas gangrene in the liver was observed following the intraperitoneal injection of sterile bile, and in seven instances fluid at autopsy was infected when

the bile at the time of injection had been sterile. Fig. 6 reveals multiple areas of necrosis of the liver containing clumps of clostridial organisms in an animal dying sixteen hours, fifteen minutes following the intraperitoneal injection of

Fig. 2.

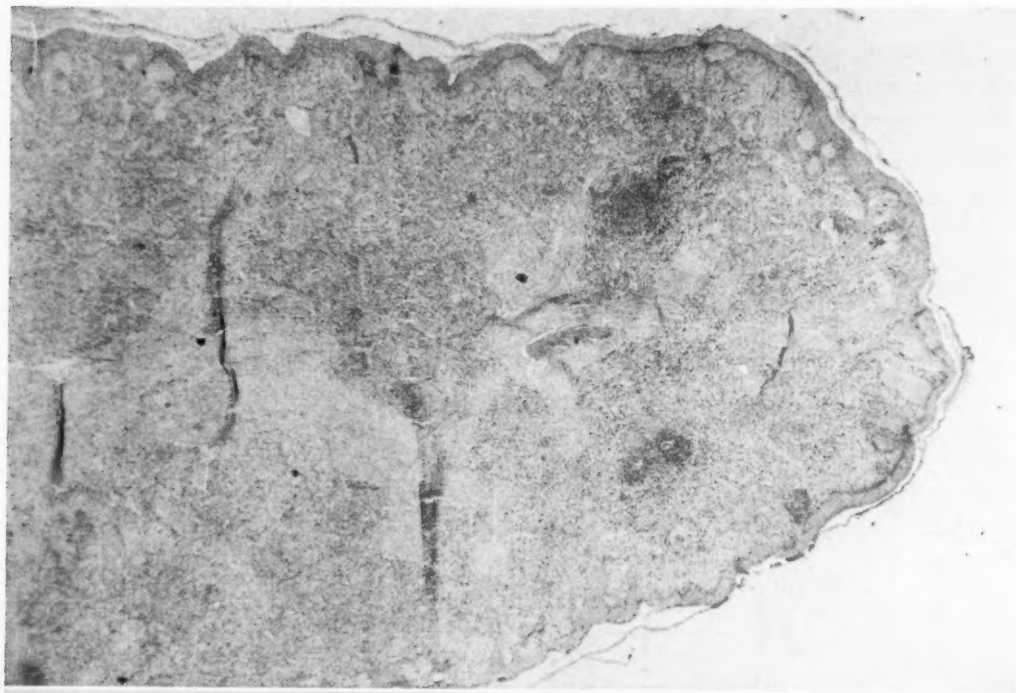


Fig. 3.

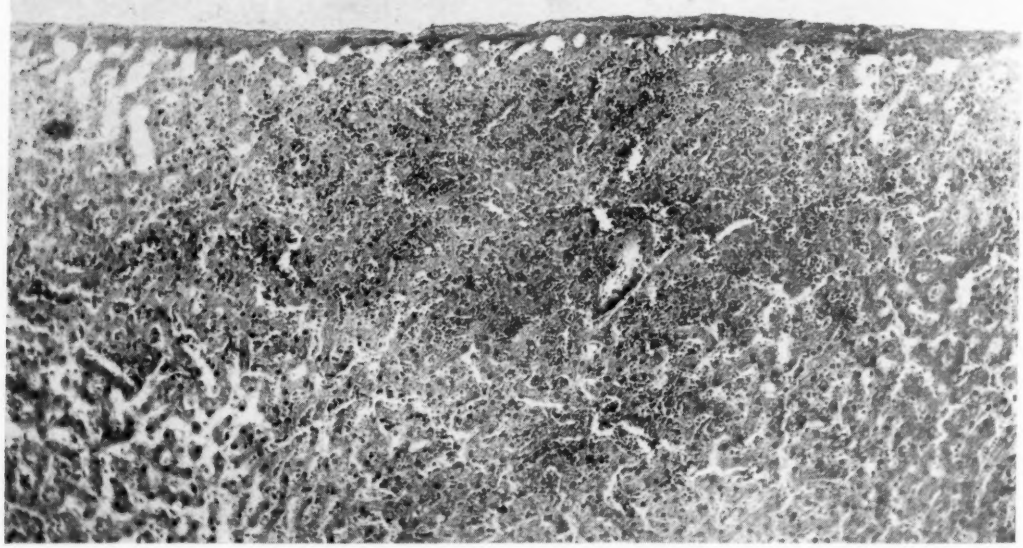


Fig. 2.—Spleen of animal sacrificed four hours following intraperitoneal injection of 23.2 c.c. of plain sterile bile per kilogram of body weight. Note intense congestion of subcapsular sinusoids.

Fig. 3.—Liver of dog dying forty minutes after receiving 30 c.c. of sterile autoclaved bile per kilogram of body weight. Section shows necrosis of capsule and parenchyma and marked congestion.

Fig. 4.

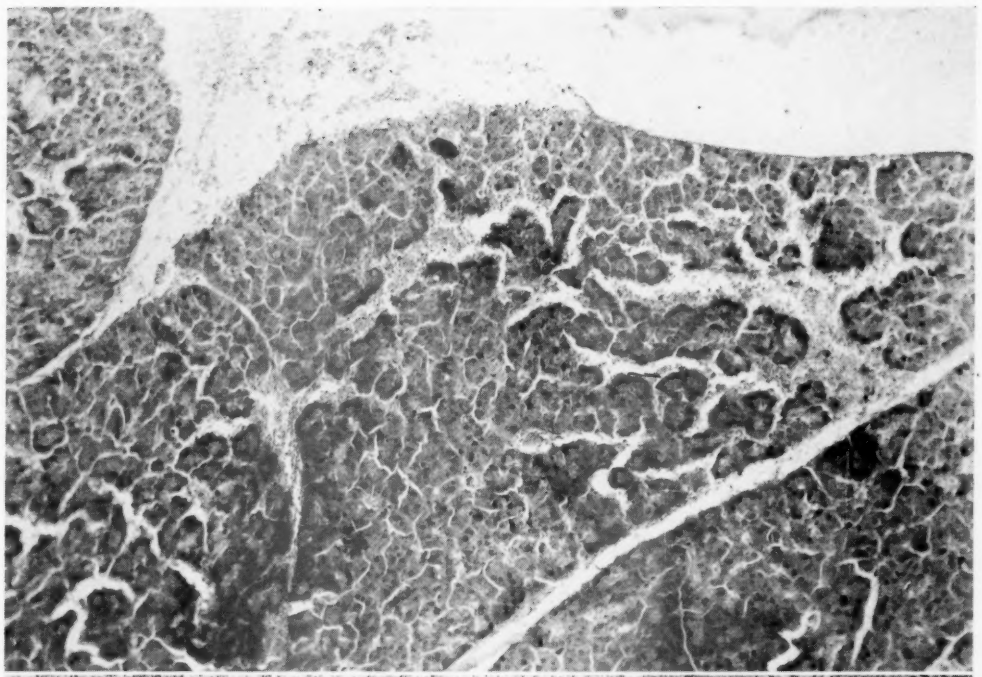
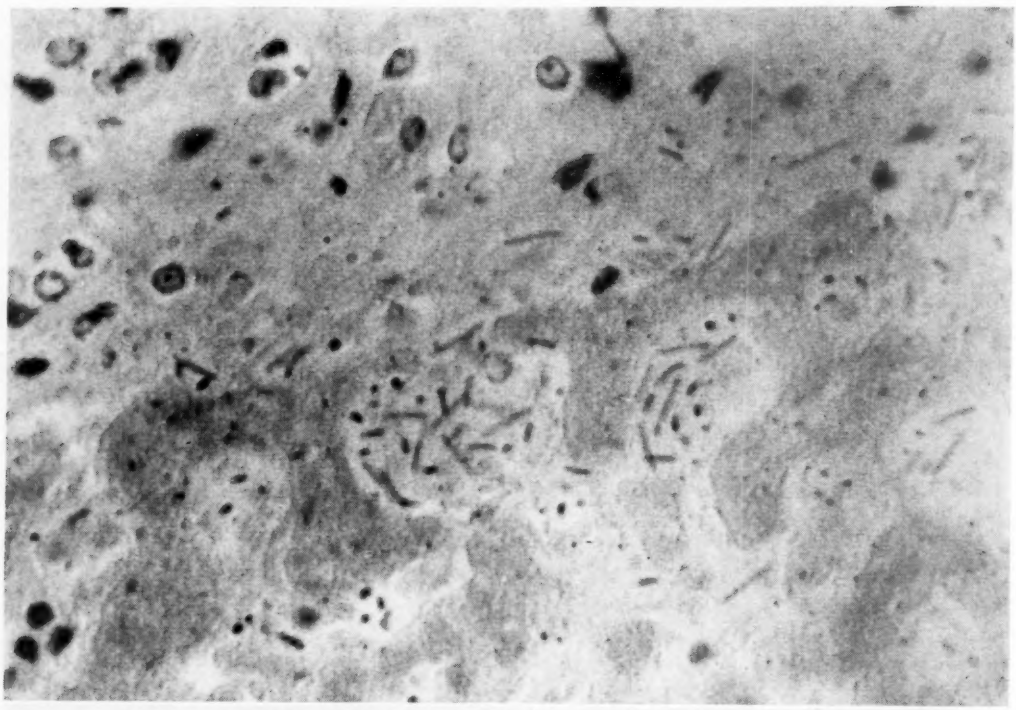


Fig. 5.

Fig. 4.—Hemorrhagic pancreatitis eleven and one-half hours after the injection of 12 c.c. of plain sterile bile per kilogram of body weight.

Fig. 5.—Section of liver showing extensive necrosis in cells near periphery. Animal died twenty-one hours after receiving 30 c.c. of infected bile per kilogram of body weight.

Fig. 6.



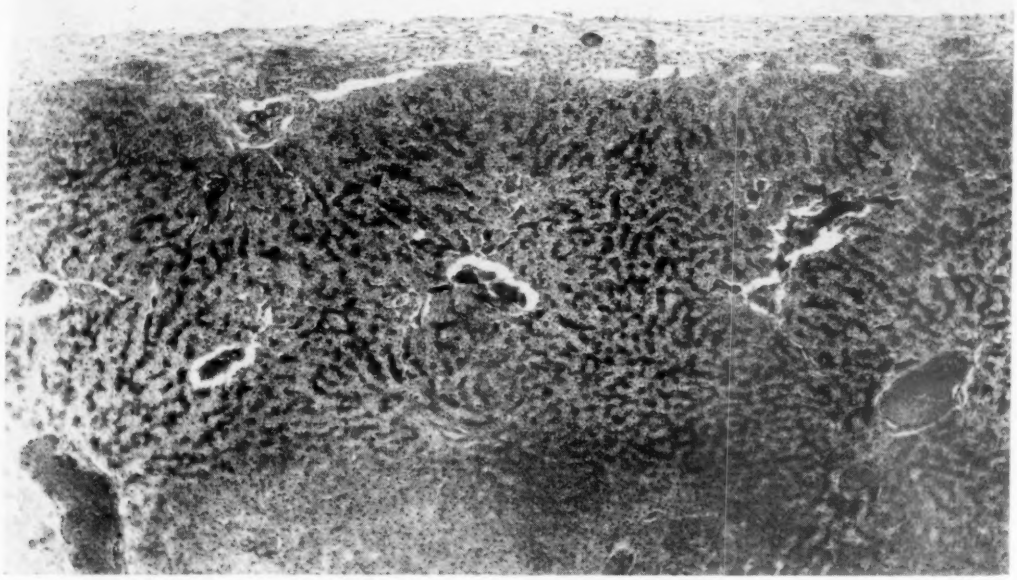


Fig. 7.

Fig. 6.—Section of liver showing clostridial organisms. Animal died sixteen hours, fifteen minutes following intraperitoneal injection of 30 c.c. of sterile autoclaved bile per kilogram of body weight.

Fig. 7.—Fourteen-day sacrifice following injection of 25 c.c. per kilogram of sterile bile. Note marked congestion of the sinusoids and fibrosis of the capsule of the liver.

sterile autoclaved bile. The absence of inflammatory reaction is striking. Most of our animals died before this stage was reached.

Other effects observed microscopically were cortical congestion and tubular degeneration of the kidneys, fibrosis and edema of the capsules and occasional congestion of the reticular layer of the adrenal glands, pulmonary congestion and occasional edema and interstitial pneumonia, and bloody mucus in the lumen of the small intestine. Hemorrhages in the adrenals, kidneys, brain, and liver and extensive subserosal intestinal hemorrhage as described by some investigators[7, 10] were not observed.

The absence of the usual inflammatory exudate was striking in that microscopic evidence of peritonitis, other than a tendency toward cuboidalization of the serosal cells, was rarely observed.

McWilliams[17] was aware that the presence of bile diminished phagocytosis. He quoted the work of Conradi who proved that the addition of bile to normal blood serum reduced its bactericidal properties. He also quoted Neufeld and Handel who suggested that the salts of bile bind the bactericidal and hemolytic complements. They observed a great decrease in the bactericidal properties of serum poured into the peritoneal cavity in response to irritation. These mechanisms may serve to explain the absence of a phagocytic response and the high mortality rate following the injection of infected bile, even in small amounts.

Of interest, pathologically, was the observation in the later deaths of large amounts of dark golden pigment within the capsules and the outer layers of the parenchyma of the liver, spleen, pancreas, and to a lesser extent the adrenals and kidneys. This probably represents absorbed bile pigment. Investigation of the nature of this pigment, which has been described by others,[3] is currently under way.

The four animals in which sterile autoclaved bile was used died. The fluid was bloody, a plastic exudate was present, and local tissue damage was much more extensive than when similar amounts of plain or penicillinized sterile bile was used.

Animals surviving the first thirty-six hours lived until sacrificed (fourteen to twenty-one days) except in three instances. No significant gross abnormalities were observed. Microscopic examination of grossly normal specimens revealed evidence of recent severe damage to the serosa, capsule, and parenchyma of the viscera. This was manifested by thickening, fibrosis, and hypertrophy of the capsules of the liver, spleen, pancreas, adrenals, and kidneys. Marked congestion of the sinusoids of the liver, spleen, and kidneys was still present (Fig. 7). Early cirrhotic changes in the liver, tubular regeneration of the kidneys, and replacement fibrosis were apparent. Large amounts of dark pigment were present in the capsules and the solid viscera.

COMMENT

The difference between our results and those of other investigators concerning the questions of lethal dose, infection, effect on the peritoneum and viscera, cholemia, and fluid loss into the peritoneal cavity may be due to differences in the technique of the production of bile peritonitis. Our experiments involved the use of plain untreated bile in 47 per cent of the animals.

In the remainder, sterility was maintained by an antibiotic which does not appear to alter the chemical composition of bile. Other investigators have used bile salt solutions in lieu of bile in a number of experiments. The use of aerobic and anaerobic culture controls at the time of injection and at autopsy may account for the difference of reported results pertaining to the importance of infection.

Bile peritonitis occurs clinically in certain cases of acute cholecystitis with or without visible perforation, in cases of trauma to the liver or biliary tree, following operations on the biliary tract, and following liver biopsy, particularly in the presence of obstructive jaundice.

In such cases the intraperitoneal extravasation of bile is often slowly developed, and this may account for survival in many cases. The bile is diluted by the outpouring of fluid secondary to peritoneal irritation and is walled off by the omentum and adhesions. Perforations of the biliary tract into the free peritoneal cavity are rare, usually occurring as the result of trauma. These are attended by high mortality[4, 20] and are most comparable to experiments in which large amounts of bile are injected.

These studies indicate infection to be of prime importance, particularly when bile in sublethal amounts is used, and are comparable to most studies of clinical cases in which bile is present in sublethal amounts and infection is present or potential. In these cases the use of antibiotics of a wide antibacterial spectrum to prevent or treat infection is mandatory.

It is suggestive that the results of these experiments are clinically applicable in emphasizing the pathologic effect of bile in the peritoneal cavity, although it may cause no visible abnormalities or, at most, only a mild peritonitis. It is extremely dangerous from the following standpoints: it may cause congestion and edema of the viscera and reticulo-endothelial system, which may lead to shock by fluid loss into these viscera; it may cause inhibition of the inflammatory response; it may have a continuous inwardly progressive local necrotizing effect on the peritoneum, capsules, and parenchymal cells of the viscera; it is virulent when associated with infection; it increases the likelihood of development of purulent peritonitis and anaerobic infections of the liver, pancreas, and spleen and of development of hemorrhagic pancreatitis; and it may make possible the absorption of toxic or lethal amounts of bile salts into the blood stream. In addition, if the patient survives he may be subject to various ills secondary to the residuals of the effects of bile peritonitis such as adhesions, cirrhotic changes in the liver, tubular regeneration of the kidneys, and replacement fibrosis of portions of the viscera.

The validity of early diagnosis, drainage of accumulations of bile, and the use of routine drainage after operations on the liver and biliary tract is indicated by these experimental findings.

The cause of death in bile peritonitis is probably due to a multiplicity of factors depending on the time interval after bile peritonitis is produced and the presence or absence of infection. The early deaths with no gross abnormalities are attributable to cholemia, which is responsible for death be-

cause of the systemic effect of the bile salts. The later deaths appear to be due to a combination of the effects of cholemia and the local necrotizing effect of bile on the peritoneum and viscera. If the bile is infected, septic peritonitis assumes major importance. Shock from fluid loss into the tissues may be a contributory factor in all instances.

CONCLUSIONS

1. The lethal dose of sterile bile injected intraperitoneally in the dog varies from 20 to 40 c.c. per kilogram of body weight.

2. Sterile bile varies in its effect on the peritoneum and viscera depending on the amount injected and the time interval after injection. At early intervals no effect may be demonstrable grossly or microscopically other than congestion of the viscera; later, bile causes necrosis of the peritoneum, capsules, and adjacent parenchymal cells of the viscera.

3. Infection is of prime importance in bile peritonitis, the mortality rate being extremely high even when small amounts are involved.

4. Deaths prior to ten hours after the intraperitoneal injection of large amounts of sterile bile are probably due to the effects of cholemia.

5. Deaths between ten and thirty-three hours after injection are probably due to a combination of the effects of cholemia and the local necrotizing action of bile.

6. When infection is present, generalized peritonitis with varying degrees of necrosis in the liver, spleen, and pancreas becomes a major contributing factor.

7. Bile in the peritoneal cavity interferes with the usual inflammatory response of the local tissues.

8. The accumulation of intraperitoneal fluid in amounts sufficient to cause death from shock appears to be of minimal importance.

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DISCUSSION

DR. DAVID V. HABIF (New York, N. Y.).—The observations reported in the paper are not quite applicable to the human being. The sudden escape of bile into the human peritoneal cavity not only causes a clinical peritonitis due to irritation but also results in a large volume of fluid collection. If sufficiently severe, the clinical picture of hyponatremia is seen: nausea, vomiting, weakness, prostration, and in some instances shock. Therapy should be directed at correcting this water and salt loss and at removal of peritoneal fluid early to prevent death.

DR. RALPH F. BOWERS (Memphis, Tenn.).—The time is short, but I wish to clarify one aspect of the work of Dr. Miles and Dr. Jeck. Dr. Miles talked about the clinical application, and the last discusser referred to it. I will briefly mention one episode. A boy was sent to us from Florida who had been injured in a tractor accident two months previously. The physician had performed paracenteses every other day. The patient was jaundiced and seriously ill. We were amazed when, by paracentesis, we obtained bile, which was probably diluted with peritoneal fluid in amounts of 5,000 to 6,000 c.c. daily. Nevertheless, the patient was not too desperately ill. Drainage was first established, which created a biliary fistula. Later, when exploration was carried out, we found that the large collection of bile resulted from a complete tear of the common duct along with rupture of the left lobe of the liver. No connection between the biliary tract and the gastrointestinal tract could be found. Choledochojejunostomy by Roux Y operation and drainage of the liver induced recovery.

It was perplexing to see a patient survive a condition where all of the bile escaped into the peritoneal cavity. The bile in the traumatized patients is not infected. There is a difference between the effect of the infected bile due to perforation of the gall bladder and of the sterile bile of trauma. The traumatized patients, therefore, fit pretty well the experiments and results obtained by Dr. Miles and Dr. Jeck with the intraperitoneal injection of sterile bile.

We postulate from this case, and a few others which time will not allow me to describe, that the period of shock induced a slow escape of bile into the peritoneal cavity, which permitted the body defenses to wall off the bile, and this walling-off procedure probably saved the patient's life and allowed us to aspirate, drain, and produce a biliary fistula following which successful transplantation of the common duct into the jejunum could be accomplished.

FLUID KINETICS FOLLOWING THERMAL BURNS IN MAN

A Preliminary Report

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ALTHOUGH it has been shown that following injury the rate of urine formation may be diminished for several days,[1, 4, 5] the urinary output is usually employed as a major guide to the administration of fluid and electrolytes in burn patients. Certainly the urinary output has been the most practical guide available. However, burn patients frequently exhibit signs and symptoms of cardiopulmonary embarrassment during the first few days of therapy. One objective of the present study, therefore, has been to examine certain of the body fluid kinetics with a view to determining whether or not the fluid and salt therapy currently given burn patients is excessive. For the purposes of this investigation, we have made the provisional assumption that a normal cardiac output reflects a reasonably effective blood volume, regardless of what the current rate of urine formation may be. If this first assumption is permissible, then the next question which arises is that of whether or not an adequate effective blood volume reflects an adequate state of hydration of the patient. Finally, since the urinary output may not be a reliable guide to therapy under all circumstances, what confidence can be placed in the brachial arterial blood pressure as a guide to the state of hydration of the patient?

Ten patients whose burns exceeded 15 per cent of body-surface area have been investigated. Selected case studies will be used to introduce the following subjects:

(1.) Evidence That Fluid and Salt Therapy Is at Times Excessive, (2.) Clinically Useful Methods for the Measurement of Cardiac Output, With Results Obtained in Normal Individuals and in Burn Patients, (3.) The Relationships Between Urinary Output, Insensible Fluid Loss, and Burn-Wound Closure, (4.) The Relation of Body Weight Changes to Urinary Output, and to Urinary Sodium Excretion, (5.) Right Heart and Pulmonary Arterial Pressures in Burn Patients.

1. *Excessive Fluid and Salt Therapy.*—

Patient J. S. (40 per cent Burn): This 30-year-old white man was burned on the lower body and legs with hot tar when his truck overturned. He was admitted to a private

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hospital thereafter and was treated by the open method. A fracture of the left femoral shaft was treated with an intramedullary pin, and a mandibular fracture was wired. The burn injury responded well to treatment in the immediate postburn period. The fluid and electrolyte therapy consisted chiefly of blood, plasma, and oral "Haldane's solution" (3 Gm. of sodium chloride and 1.5 Gm. of sodium bicarbonate per liter of water). The areas of second and third degree involvement were covered with a layer of early eschar by the end of thirty-five hours, and by the end of forty-eight hours weeping had practically ceased. Clinical progress was satisfactory until the sixth postoperative day when the patient became markedly dyspneic and required oxygen therapy. It was found that the blood pressure had risen from a previous level of 120/80 to 182/84. Rales were present throughout both lung fields, and generalized edema was observed, with marked penile and scrotal involvement. The fluids which the patient had received had been carefully recorded and are shown in Fig. 1.

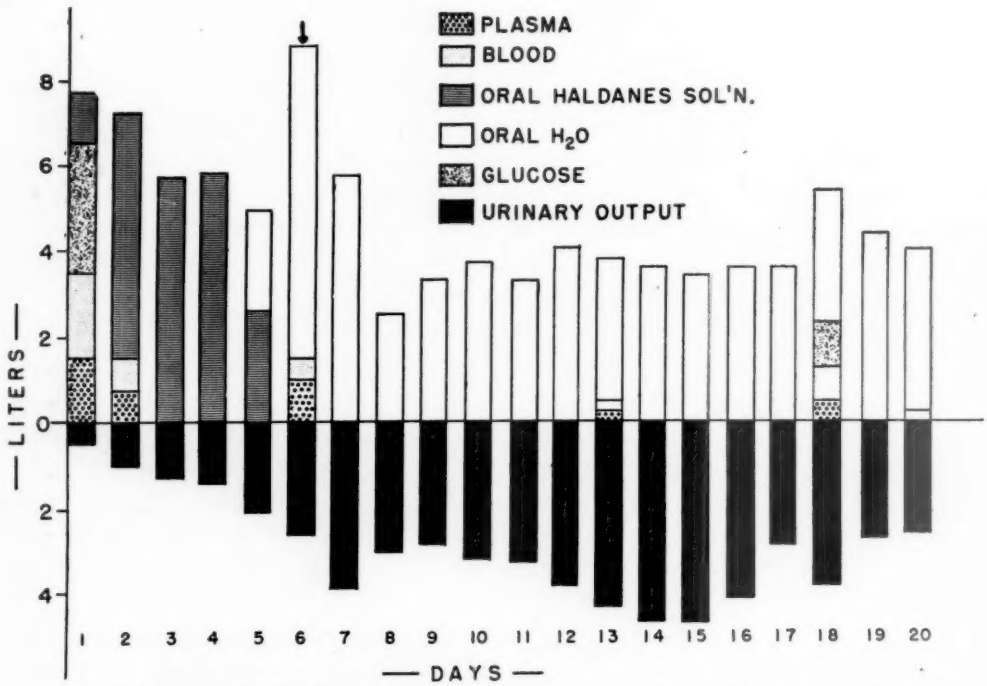

Fig. 1 (Patient J. S., 40 per cent burn).—Fluid intake and urinary output. This chart indicates the large volume of fluid, particularly of oral "Haldane's solution" (3 Gm. of sodium chloride and 1.5 Gm. of sodium bicarbonate in a liter of water), which this patient received prior to the onset of pulmonary râles, dyspnea, and hypertension on the sixth day. He became markedly edematous. On the seventh day the fluid and electrolyte intake was reduced and was for a time limited to water and the salt in his food. Thereafter, despite daily atmospheric temperatures of from 100° to 106° F., the urinary output tended to equal or to exceed the liquid intake for almost ten days, during which period the generalized edema subsided. The water provided by metabolic oxidation of the limited amounts of food which the patient consumed during this period has not been charted. The burns were treated by the exposure method, and weeping had practically ceased by the end of forty-eight hours following injury.

It seemed clear to the consultant, who first saw the patient on the seventh postburn day, that the patient's cardiopulmonary distress was a result of the large amounts of salty fluid which he had recived for the first five days. In planning therapy, little account had been taken of the fact that after forty-eight hours the wounds had crusted over and that this had probably diminished the fluid requirements. It was recommended that water and, particularly, salt therapy be limited for the ensuing forty-eight hours. The dyspnea diminished within twenty-four hours. Moreover, despite the fact that the atmospheric temperature was rising to daily peaks of from 100° to 106° F., the urinary output approximated or exceeded the fluid intake for almost ten days following the withholding

of salty fluids (Fig. 1). The edema began to subside at the same time that the urinary output increased, but this drying-out process was not complete until approximately two weeks following the burn injury.

Comment: This clinical case study is included in this report because it focuses attention upon one of the basic questions which prompted this study, namely, whether or not there is a tendency at the present time to overtreat burn patients. This patient was unquestionably overtreated, especially after the first forty-eight hours. The loss of fluid and salt into the tissues surrounding the burn wounds and through the burn surfaces did not nearly approximate the amounts of fluid and salt administered. Daily weight measurements would have afforded useful information regarding rates of "insensible fluid loss"* in this patient, but because of the femoral fracture he could not stand, and litter scales were not available at his hospital.

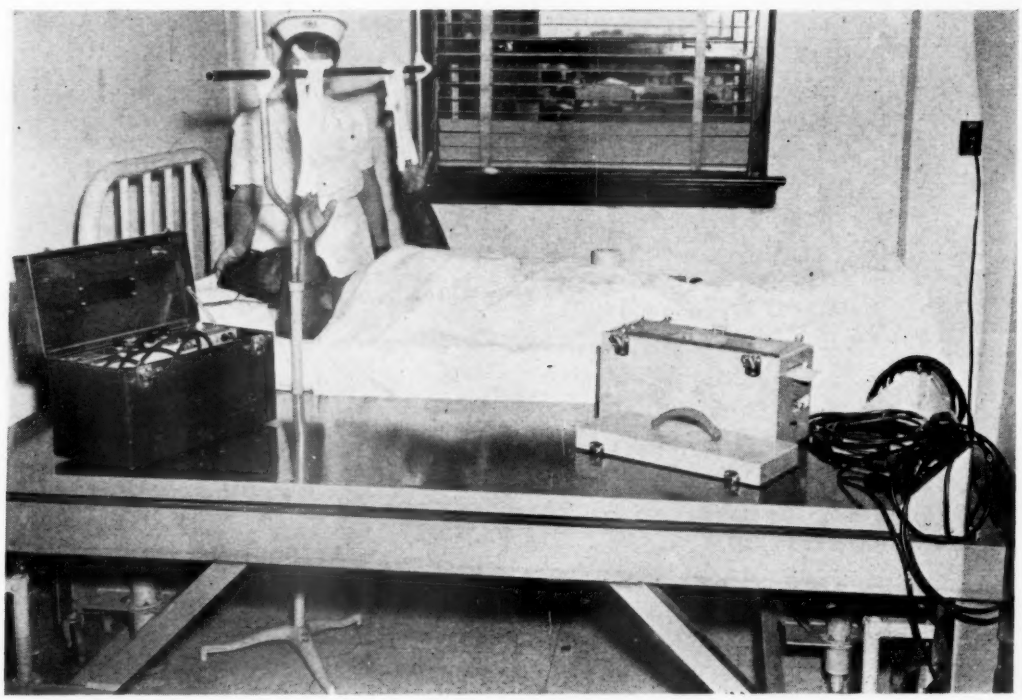

Fig. 2 (Patient T. S.).—The ballistocardiograph for measuring cardiac output. This photograph shows the ballistocardiograph in the foreground with the electrocardiograph and the two-channel recorder resting on the table. To determine cardiac output, the patient is placed on the table in the supine position with feet pressed firmly against the foot rest. The slight downward movement of the body with each heart beat, caused presumably by the heart's ejection of blood against the curve of the aortic arch, is magnified and is recorded on paper which resembles that of the electrocardiograph (Fig. 3, upper tracings). Simultaneously, the electrocardiogram is recorded on the lower portion of the double-channel paper, and this tracing serves as a timer.

Another patient, G. S., developed dyspnea on the fifth day and was digitalized on the seventh postburn day when physical examination and roentgen examination revealed congestive changes. However, he was 59 years old,

*"Insensible fluid loss," as referred to in this paper, represents the daily changes in body weight which could not be accounted for by taking into consideration only the fluid intake and the urinary output. The following formula presents our method of estimating "insensible loss": Intake = weight change (in kilograms × 1,000) + urinary output + insensible loss.

much older than patient J. S., and the impression was that, while he probably was not significantly overtreated with fluid and electrolytes, the cardiovascular apparatus was not able to cope unaided with the large amounts of fluid required for the treatment of the extensive burn.

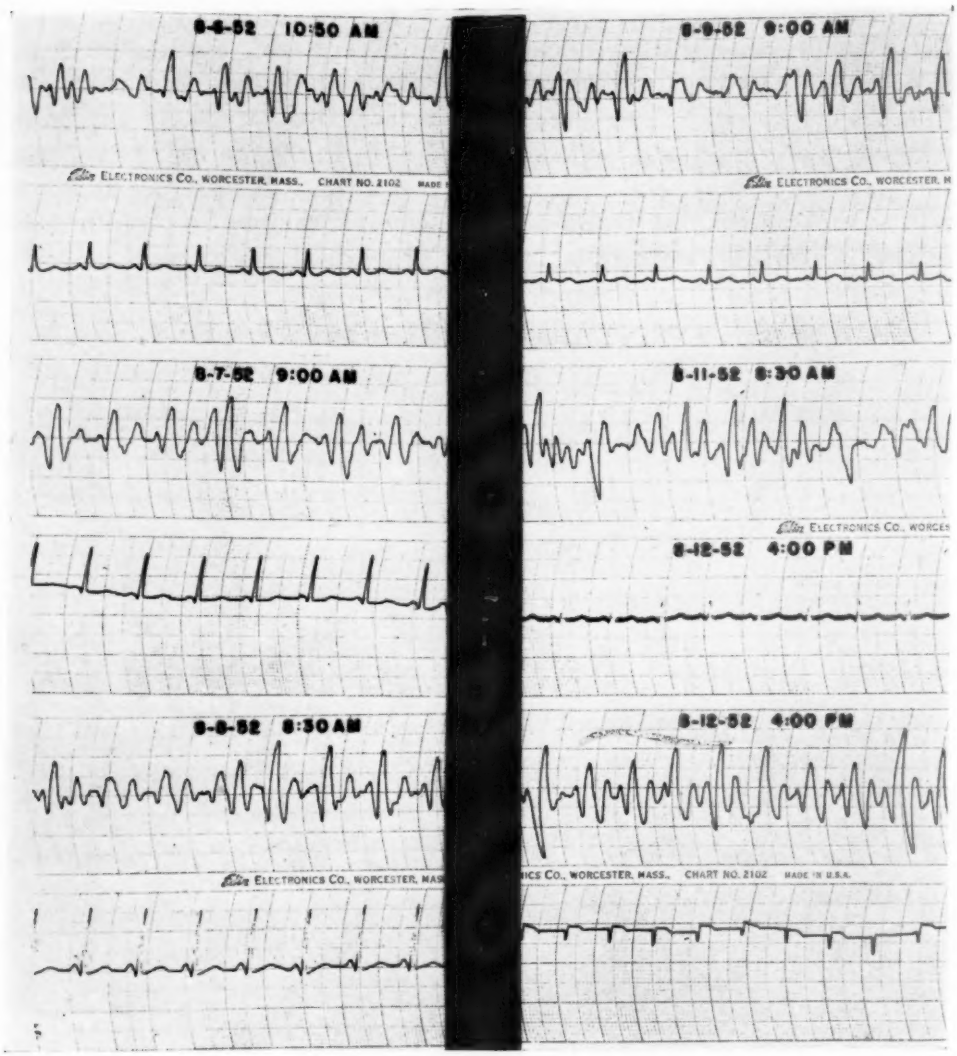

Fig. 3 (Patient J. H.).—Serial ballistocardiograms, upper tracing of each record. If the pulse rate remains unchanged, the changes in cardiac output will be proportional to the height of the complexes; that is, the greater the stroke volume, the greater will be the downward displacement of the body on the table, and the higher will be the complexes reflecting this excursion. Cardiac output is calculated by measuring with a planimeter the area beneath certain of the ballistocardiogram complexes and substituting these values in Tanner's modification of Starr's original formula $Sv = 100 \sqrt{(\int Idt + \int Jdt)\sqrt{C}}$. The electrocardiogram in these instances was taken merely to serve as a timer for the ballistocardiograph complexes, and no consistent policy was followed regarding which of the several electrocardiographic leads was to be recorded for this purpose. In fact, in burn patients it is frequently difficult to find a suitable unburned site for the application of the electrodes.

2. *Cardiac Output Measurements.*—Cardiac output measurements have been obtained in eight burn patients (Table I) and in four other patients (Table II). The ballistocardiograph[6] (Figs. 2 and 3), cardiac catheterizations with

Fig. 4.—Measurement of cardiac output by means of cardiac catheterization and the direct Fick technique. The direct Fick procedure has long been used as a reference method. In the photograph, one worker has maneuvered the sterile cardiac catheter through the basilic vein into the right heart and out into the pulmonary artery under fluoroscopic guidance. Usually this is not a difficult feat to accomplish. Through this catheter samples of mixed venous blood are drawn. The second worker seen is drawing a sample of arterial blood from the femoral artery. The oxygen consumption per minute is measured with a basal metabolic rate machine or by some other method. The formula used is:

$$\frac{\text{cubic centimeters of oxygen consumed per minute}}{\text{Arterial } O_2 - \text{venous } O_2} \times 100 = \text{cardiac output per minute in cubic centimeters.}$$

Thus C. O. $= \frac{240 \text{ c.c. } O_2}{18\text{–}12} \times 100 = 4{,}000$ c.c. or 4 liters.

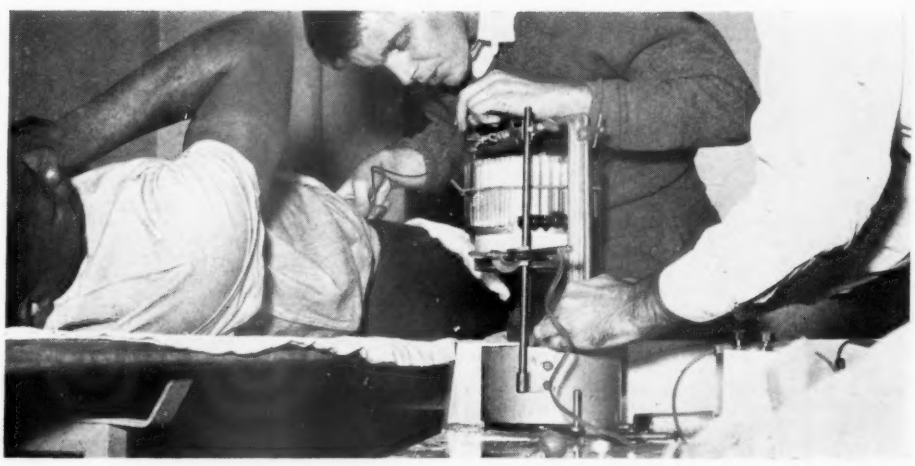

Fig. 5.—The dye method for measuring cardiac output and plasma volume. After a polyethylene catheter or a needle of the Cournand type has been threaded into a femoral artery, the kymograph drum with the affixed tubes containing heparin is started, and a carefully measured quantity of 0.5 per cent Evans blue dye is rapidly injected into an antecubital vein or into an indwelling cardiac catheter. Serial arterial samples are then collected at approximately one-second intervals over a period of from thirty to forty seconds. The tubes are then centrifuged and the plasma dye concentrations are read in the spectrophotometer. The values thus obtained in milligrams per liter are plotted on semilogarithmic paper against time in seconds. A typical curve is shown in Fig. 6.

application of the direct Fick principle (Fig. 4), and the Evans blue dye techniques[3] (Figs. 5 and 6) have been used. In some burn patients two or more of these methods have been used, and in the future it is anticipated that all three will be used, except where it is not feasible to place the patient on the ballistocardiograph. In each burn patient the values for cardiac output have been above the lower range of normal. No patient has been in shock at the time studied except G. S., and his hypotension was only moderate (94/66).

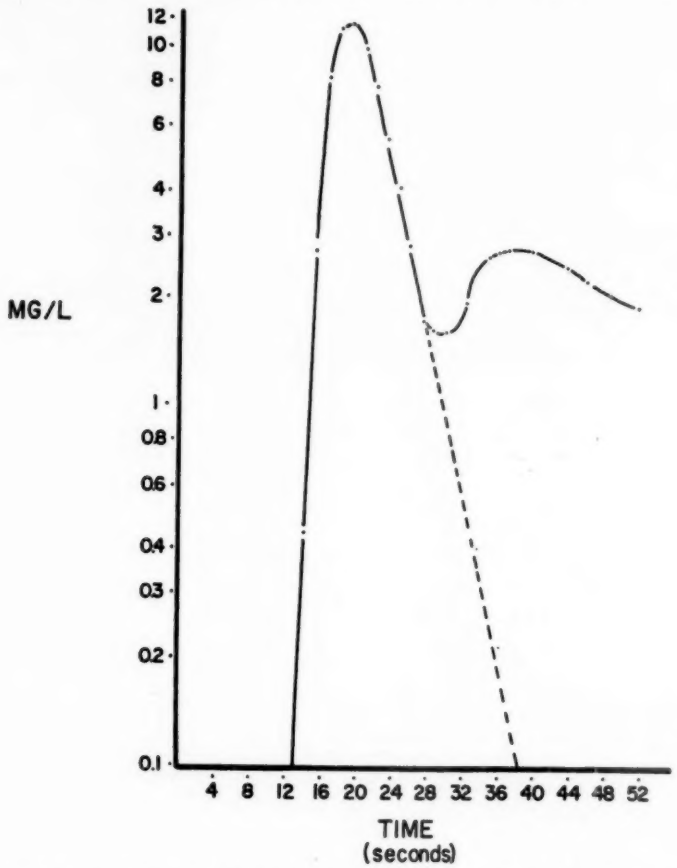

Fig. 6.—Typical curve obtained using the dye method for cardiac output. Cardiac output is calculated from the area beneath the curve as indicated. It will be noted that the decay portion of this curve forms a straight line until recirculation of the dye begins. By extrapolating this line to the base line, one gets a very close approximation of what the curve would have been if no recirculation had occurred. By measuring the height of this curve at one-second intervals throughout its entirety and adding these values, a sum (S) is obtained. The cardiac output is then calculated by substituting in the following formula:

$$\text{C. O.} = \frac{60I}{S(1\text{-HCT})}$$

where I represents milligrams of dye injected. Plasma volume also may be obtained from this curve.

In general, the following comments may be offered concerning the three methods for measuring cardiac output: The ballistocardiograph is not suited to use in most burn patients because of the variable sites of burns and the inability of severely burned patients to remain still. The direct Fick method, utilizing cardiac catheterization, is applicable to burn patients when both arms are not involved, but the number of separate measurements which can be

undertaken on any one patient is limited. The dye method is one which offers much promise. It is simply performed and it lends itself to multiple measurements in the same patient. This is a method which we now believe will be a most useful one in the study of burn patients.

Fig. 7 (Patient L. O., 22 per cent burn).—This patient, burned with hot grease, was treated by the open method. On the twelfth and fourteenth days he shed the two halves of the leathery crust visible in the photograph, to reveal a completely epithelized surface beneath. It appears that when patients can be treated by the open method the excessive insensible fluid losses are amenable to more prompt control, and that the need for skin grafting may be reduced. The latter may reflect a somewhat lower incidence of severe wound infections, in addition to the avoidance of the local (and the psychic) trauma often associated with the dressing of burn wounds.

3. *Relationship Between Urinary Output and Insensible Fluid Loss.*—

PATIENT L. O. (22 per cent Burn).—This 28-year-old Negro man was burned with hot grease on back, shoulders, and upper arms. Since the burn areas were limited chiefly to the posterior or extensor surfaces, it was possible to treat this patient with the open or exposure method, and in Fig. 7 it may be seen that the wounds became covered with a leathery

crust which had formed by the fourth postburn day. Daily weights were obtained on this patient with the litter scales shown in Fig. 8. In Fig. 9 it may be seen that prior to the time the wounds crusted over the insensible loss exceeded the urinary output; after the wounds had crusted over, the urinary output exceeded the insensible loss.

Comment: The increase in urinary output might have occurred at this time regardless of insensible loss, for a diuresis is often observed beginning on

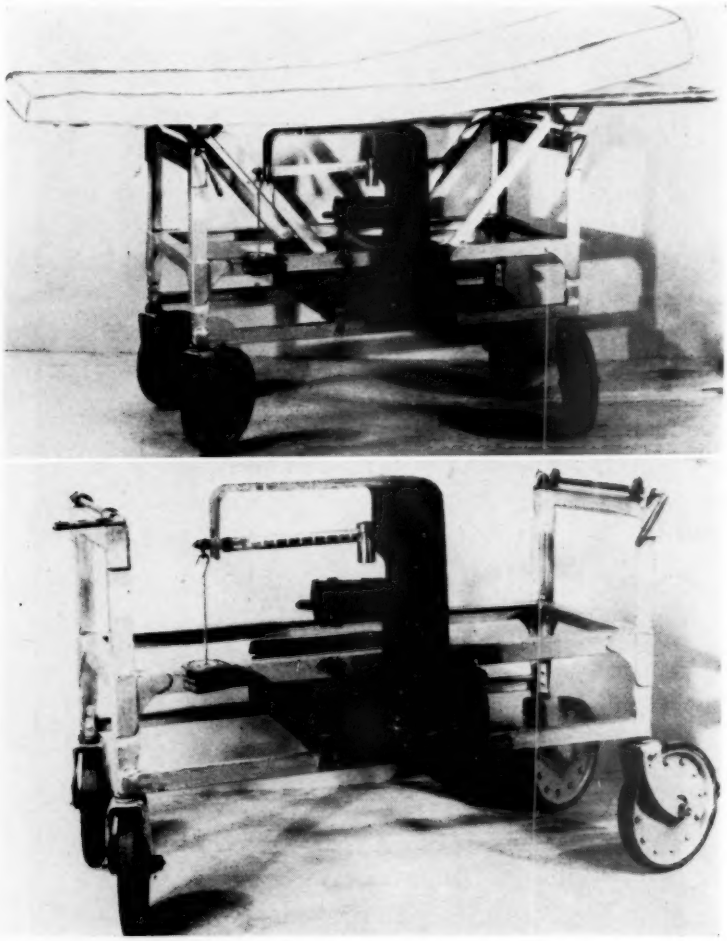

Fig. 8.—Rolling litter scales for bedside weighing. These scales are accurate to within less than 50 grams. They have been found to be sturdy and most useful.[8]

about the fifth to the seventh day, regardless of whether the patient is treated by the open or closed method. However, daily weights in two additional patients treated by the open method have indicated a definite decrease in insensible fluid loss after the burn wounds crusted over. Thus, it is apparent that after burn wounds crust over the fluid requirements will be less and that therapy should be modified accordingly. We are beginning to believe that patients treated with the exposure method, who crust over, afford earlier control of fluid losses than do those patients whose burn wounds are dressed. It is also our tentative impression that to cover a burn with gauze dressings increases the likelihood that the wound will require grafting, this being the result of the in-

evitable trauma, maceration, and infection which destroy remaining islands of epithelium. Patient L. O. (Fig. 7) was thought certain to require extensive grafting, but when he shed the two halves of the leathery eschar on the twelfth and the fourteenth days, it was found that the underlying surface was completely epithelialized.

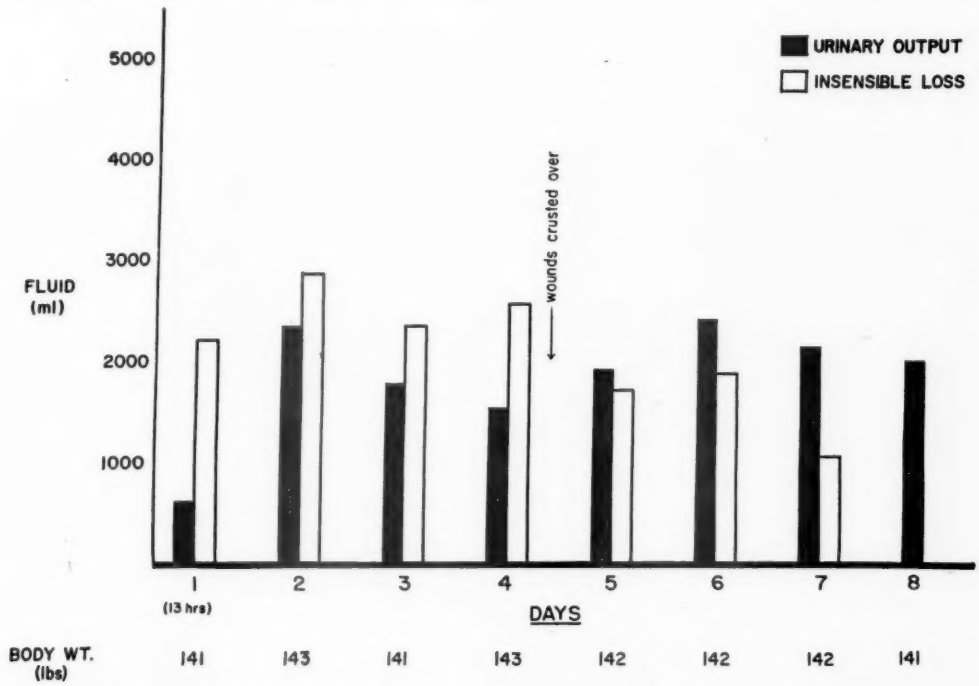

Fig. 9 (Patient L. O., 22 per cent burn).—Fluid balance; urinary output and insensible fluid loss. This chart shows the relationship which existed in this patient between urinary output and insensible fluid loss. He was treated by the open method, and his weight was determined daily. The value for insensible loss was obtained by substituting in the following formula: Fluid intake = body weight change + urinary output + insensible loss. Three of the four values are known, thus allowing ready computation of the unknown, insensible loss. This formula ignores body weight change due to tissue metabolism, but it is believed that the loss of body tissue each twenty-four hours is of small magnitude when compared with the relatively large changes in water exchange which occur in the early days of treatment of burn patients. Note the decrease in insensible fluid loss after the wounds crusted over on the fourth day. Before this time the daily insensible fluid loss exceeded the urinary output but thereafter the reverse was true. (The first "day" represents a period of only 13 hours.) A prompt decrease in insensible fluid loss following the crusting over of the wounds was noted in three other burn patients treated by the open method.

4. *Correlation Between Body Weight Changes, Urinary Output, and Urinary Sodium Excretion.*—

Patient R. J. (55 per cent Burn, 45 per cent Third Degree): This 27-year-old Negro man was injured when gasoline fumes exploded and burned his house down. He sustained severe burns of the back, hands, and legs. In addition, there were deep second-degree burns of the face and neck (Fig. 10). It was not feasible to treat him entirely by the open method, and the soaked dressings made it impossible to obtain accurate body-weight measurements daily. However, he was weighed on admission and then again each time that the dressings were removed. In this way a reasonably satisfactory body-weight curve was achieved (Fig. 11). During the first forty-eight hours the patient's weight increased from the admission value of 150 pounds (68 kilograms) to 173 pounds (78 kilograms). The volume of fluid he required was estimated more or less according to the formula suggested by Evans.[2] Despite a marked weight gain, associated with the appearance of marked edema both adjacent to the burned areas and in distant parts of the body, the urinary output remained at a daily

volume of about one liter until the sixth day. During this time, the urinary output of sodium was low. However, beginning on the sixth day the urinary volume and the urinary sodium content began to increase. The increased urinary excretion of sodium persisted until the thirteenth day, after which it began to subside. During this period of sodium and water diuresis the clinical edema also began to subside and the body weight returned to

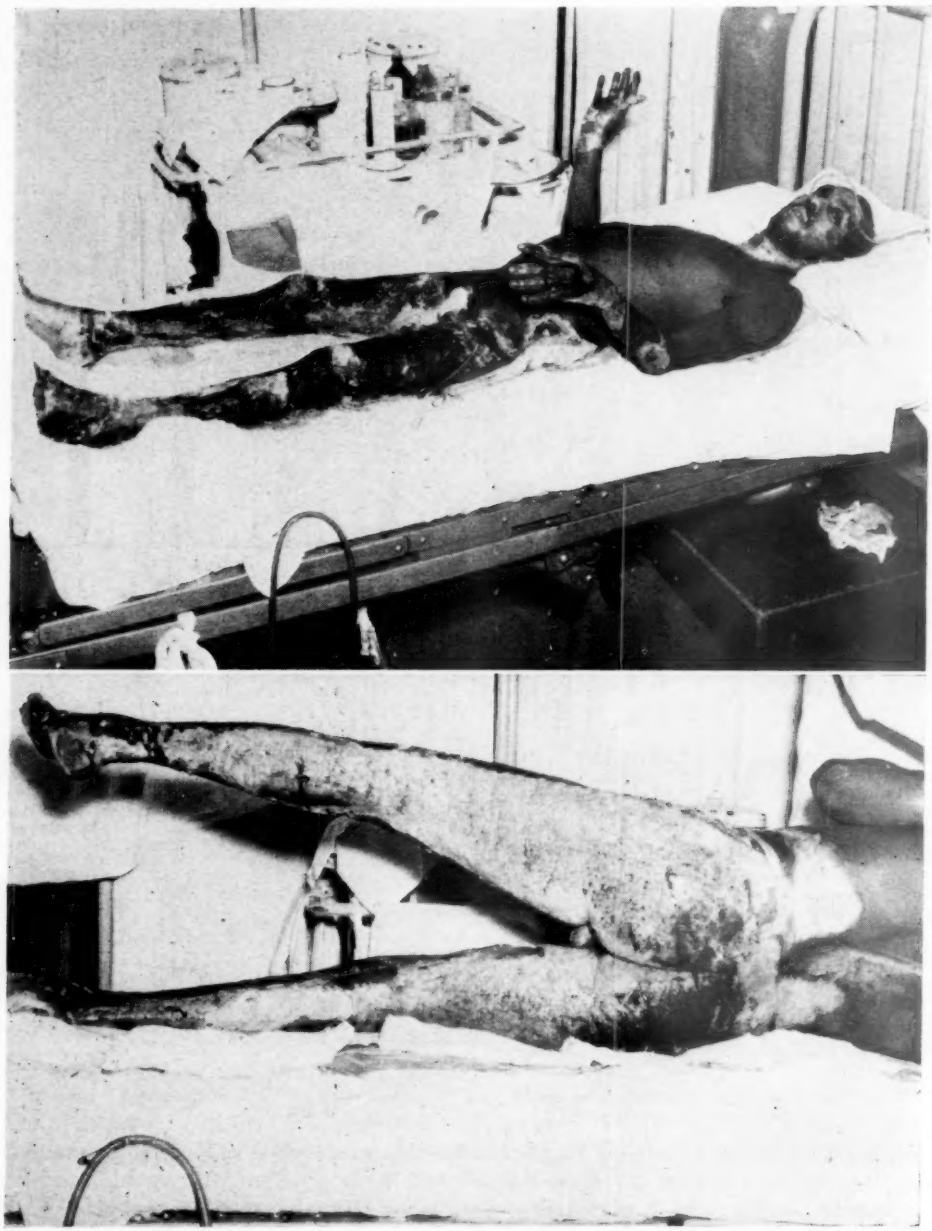

Fig. 10 (Patient R. J., 55 per cent burn [45 per cent third degree]).—This patient sustained extensive burns when gasoline fumes exploded and burned his house down. He lived for thirty-nine days, but his sensorium was never really clear from the time he was injured. The major problems encountered in the management of this patient were those of fluid balance, nutrition, and severe infection. It is now possible to sustain most burn patients through the stage of shock, but the problems of nutrition and of refractory wound infections are far from being solved.

normal, before continuing downward because of tissue losses. The sodium intake in this patient was measured, but the losses through the burn-wound exudate and stools were not measured.

In general, our most severely burned patients have begun to diurese on about the fifth to the seventh day, and the abnormal fluid deposits have usually been eliminated by the end of about two weeks.

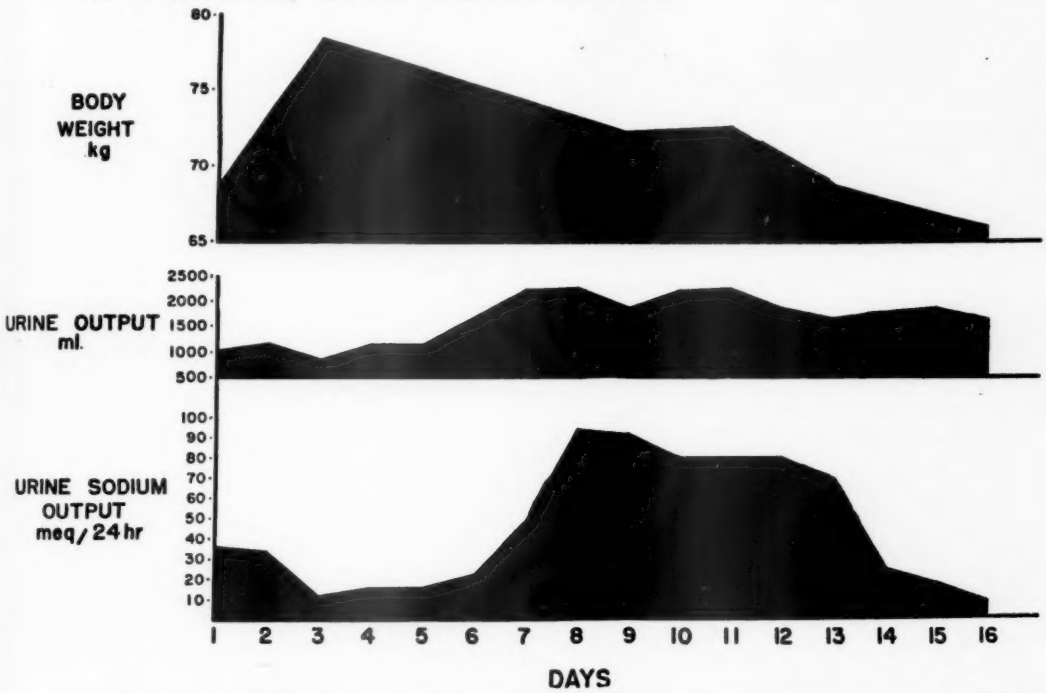

Fig. 11 (Patient R. J., 55 per cent burn).—Body weight changes, urinary output, and urinary sodium excretion. During the first three days of therapy the body weight rose from an admission value of 68 kilograms (150 pounds) to 78 kilograms (173 pounds). During this period of excessive hydration the daily urinary output remained at about 1 liter and the daily urinary sodium excretion ranged from about 15 to 35 meq. On the sixth day, however, both the urinary output and urinary sodium excretion began to rise, and the decrease in body weight became accelerated. The decrease in body weight after the peak on the third day was, of course, due partly to the large insensible fluid losses which this patient suffered. By the thirteenth day the sodium diuresis and the water diuresis had begun to subside. At this time it was noted that the generalized edema had disappeared and that the body weight had returned to the admission level. In general, our most severely burned patients have begun actively to diurese on from the fifth to the seventh day and have completed this diuresis by the thirteenth to the sixteenth postburn day.

5. *Pulmonary Arterial Pressures in Burn Patients.*—Satisfactory measurements of various intracardiac, pulmonary arterial, and pulmonary capil-

TABLE I. CARDIAC OUTPUT IN BURN PATIENTS (DIRECT FICK)

PATIENT	AGE (YEARS)	SEX	PER CENT BURN	POSTBURN DAY OF C.O.*	VALUE FOR C.O.	CONTROL C.O. (6 MONTHS LATER)
J. H.	27	M	55	5	6.84	5.2
T. S.	45	F	17	1	5.91	
L. O.	28	M	22	10	4.8	
R. J.	27	M	55	2	4.94	
O. H.	19	M	25	0.5	8.65	
M. R.	23	F	23	2	20.0(?)	
M. L.	44	M	18	2.5	3.55	
G. S.	59	M	35	0	4.63	

*C. O. = Cardiac output (liters per minute).

TABLE II. CARDIAC OUTPUT IN NORMAL SUBJECTS BY THREE METHODS

SUBJECT	DIRECT FICK (LITERS PER MINUTE)	DYE (LITERS PER MINUTE)	BALLISTOCARDIOGRAMS (LITERS PER MINUTE)
W. G.	3.97	4.84	3.58
R. L.	7.25	5.63	7.17
J. H.	5.2	8.3 (turbid plasma)	7.6
R. M. B.	5.2	4.78	5.12

TABLE III. PULMONARY ARTERIAL AND CARDIAC PRESSURES*

PATIENT	PULMONARY CAPILLARY PRESSURE		PULMONARY ARTERIAL PRESSURE				RIGHT VENTRICULAR PRESSURE				RIGHT AURICULAR PRESSURE	
			SYSTOLIC		DIASTOLIC		SYSTOLIC		DIASTOLIC			
	MAXIMUM	MINIMUM	MAXIMUM	MINIMUM	MAXIMUM	MINIMUM	MAXIMUM	MINIMUM	MAXIMUM	MINIMUM	MAXIMUM	MINIMUM
J. H.	23	8	44	29	26	8						
T. S.			32	23	14	8	32	23	2	-4	3	1
L. O.							44		2		5	-1
R. J.											2	-4

*Measurements are in millimeters of mercury.

lary pressures have been obtained in four burn patients (Table III). These results have been essentially within normal limits, and thus impending cardiac failure would not appear to have been present in these patients. None of these patients was in shock at the time studied.

SUMMARY

1. Certain fluid kinetics have been studied in ten patients whose burns exceeded 15 per cent of body-surface areas.

2. The observations and measurements performed included the clinical course, fluid intake, urinary output, body weights, urinary sodium excretion, right heart and pulmonary arterial pressures, and measurements of cardiac output by means of the ballistocardiograph, dye, and direct Fick methods.

3. The three methods for the clinical measurement of cardiac output are compared. Early results indicate a fairly good correlation between the values obtained in normal subjects by the three methods. Cardiac output values obtained in burn patients have been above the lower limits of normal.

4. The dye method for measuring cardiac output is particularly suited to clinical use.

5. Evidence is presented which indicates that burn patients may be overtreated with fluids. This further substantiates the well-recognized fact that after the first forty-eight to seventy-two hours the amount of fluid and electrolyte administered to burn patients should be sharply reduced.

6. In the most severely burned patients that we have studied, there has been a tendency for the diuresis to begin on the fifth to the seventh day and to be completed on the thirteenth to the sixteenth day. There was a concomitant sodium and water diuresis in the one patient placed on a partial sodium balance study.

7. The rate of insensible fluid loss varies considerably from one burn patient to another and in the same patient from day to day.

8. Pulmonary and right-heart pressures were not abnormal in three burn patients so studied.

9. It is perhaps worth re-emphasizing that the systolic blood pressure, used in conjunction with the urinary output, is still a most useful guide to fluid therapy in severely burned patients.

Acknowledgments.—The assistance of many members of the professional and nursing staffs of The John Gaston Hospital is appreciated. We wish especially to acknowledge the cooperation and clinical assistance of Drs. Charles E. Guice, Stephen R. Roddy, J. T. Duncan, and Leigh K. Haynes.

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DISCUSSION

DR. WILLIAM A. NEELY (Memphis, Tenn.).—Obviously, a number of problems remain unsolved in the investigations which have been mentioned. Among the studies which we hope to accomplish in the future are careful comparison of the three methods of cardiac output in shock. Further studies of the time relationship involved in the mobilization of sodium chloride and water in burned patients will be made. The fluid dynamics in patients treated by the open method will be compared with those of patients treated by the closed method.

INVESTIGATIONS INTO THE ROLE OF HEPARIN IN PROLIFERATIVE TISSUE REACTIONS

I. Increased Heparin Tolerance in Patients With Burns and Keloids

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THE basic fundamentals which initiate and control wound repair are as yet not established. Certain local physical factors[1-3] and some systemic factors[4, 5] are well known and form the basis for the therapeutic measures including the use of radiation therapy[6] now empirically employed.

The mechanism of normal wound healing implies that an orderly phase of inhibition follows an initial stimulation. In excessive fibroblastic proliferation either phase could be fundamentally at fault. This "accelerator and brake" mechanism may exert forces (1) by activity in the locale of the wound, according to recent description[7] of the tremendous fibroblastic growth potential produced in animals by the stimulus of foreign bodies in healing wounds or (2) by a general process related to early and late endocrine changes.[8, 9]

Investigation of stimulator substances in the serum or leukocytes of patients during the active phase of formation of hypertrophic scars and keloids was the basis for earlier studies in this laboratory. Preliminary evidence[10] that fibroblastic proliferation was stimulated in vitro by adding active phase sera of patients to animal and human tissues has not been borne out to statistical significance by further experimentation. Difficulties may be technical ones involved in tissue culture[1] and they may involve activity and concentration of test substance as well as evaluation of the clinical phase of the patient.[3] Although extracts of leukocytes stimulated fibroblastic growth according to Carrel,[11-12] no specific stimulator substance was found in leukocytic extracts made from the blood of our patients with keloids, granulating wounds, or recently healed burns. In search of more potent substances, we have resorted to electrophoresis to pick appropriate fractions of blood and tissue.

Electrophoretic analysis of the sera of eight patients here with keloids or hypertrophic scars in an active phase have been studied by fifteen electrophoretic tracings.† The electrophoretic pattern suggested an elevation of the β-globulin fraction, a beta anomaly, or an unidentified component with mobility between the beta and gamma globulin. This seemed to indicate a fibrinogen abnormality,

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†Electrophoretic patterns were made in the Department of Biochemistry, University of Kansas, Lawrence, Kan.

and associated with this is the even more consistently deficient albumin component. However, delay in some of the readings (one to three months after the blood was drawn) may prove to be a misleading factor.

Our current investigations relate to the inhibition mechanism, or rather to its inadequacy; we must determine, first, its existence and, then, its probable role. Excessive fibroblastic proliferation might be an expression of the lack of an available active inhibitor. The inhibition of connective tissue growth by adrenal cortical activity caused by the stress stimulus of the original trauma seemed a possible explanation.[8-9] The role of tissue mast cells in this process has been suggested.[13] From experiences with certain mesenchymal reactions, including the study of keloids,[14-15] the role of heparin has been emphasized by observations on tissue mast cells which are the source of heparin.[16-17] These cells are numerous near regions of cellular activity,[14-18] and large numbers are seen in granulation tissue.[15-19] In the healing of skin wounds, an inhibitor substance which has basic dye-binding capacities has been found in aqueous extracts of the wound tissue;[19] the peak in this basic dye-binding substance followed the reappearance of tissue mast cells in the granulating areas from which they had disappeared in the early acute phase of reaction in normal wounds. Heparin is a water-soluble, complex acid mucopolysaccharide, a polyester of sulfuric acid.[16]

Inhibition of fibroblasts observed in our tissue culture laboratory is consistent with the inhibitory effect of heparin on cell division.[20-23] Heparin, in our experiments, produced inhibition in vitro in concentration of 40 mg. per cent or above. Heparin added to homogenized liver released a gel[24] and affected an increase in viscosity; this was not related to anticoagulant activity. Further interpretation regarding the effect of heparin is that it combined with basic proteins of the nucleus with the displacement of desoxyribonucleic acid.

Collagen has appeared to be formed from the cytoplasm of maturing fibroblasts.[26-29] Re-formation of collagen fibers in vitro has been demonstrated in homogeneate of collagenous tissue, such as dura of babies, after addition of even dilute heparin.[25] Extracellular metachromasia in healing wounds was not correlated with the number of tissue mast cells;[30-31] many believed, however, that much of this material does come from mast cells, although this basic dye-binding acid mucopolysaccharide has not as yet been identified in the tissues definitely as heparin. Collagen might be formed by this substance which appears simultaneously with the production of intercellular fibers[32]; vitamin C appears to be necessary in this process, and may have an effect on the adrenal cortex.[33]

The observation has been reported that the clotting time of blood is increased after stress.[13] Tissue mast cells are said to pour out heparin after the injection at thrombokinase.[34] Destruction of mast cells with release of heparin has been observed in tissues treated with cortisone.[35] The 11-oxysteroid fraction released from the adrenal cortex is said to change the mast cells. After total body exposure to roentgen irradiation, an anticoagulant thought to be heparin has been found in the blood of dogs which showed a hemorrhagic tendency.[36] Radiation which is administered to prevent keloid or excessive scar formation is partially efficacious.[6] The mechanism of this action is not clear.

Heparin tolerance studies upon patients during acute phase of rheumatic state have shown some consistently abnormal findings[37, 38] which correlate with other clinical laboratory data indicating cellular activity.* Similar is the preliminary report in patients with burns and keloids.

The association of approach to problems of keloid formation and of rheumatic state has been purposeful and designed for study in our long-range program. The possible analogy between the two proliferative processes involving mesenchymal tissue is intriguing in that, once the pattern of response had been established in the patient and his host tissue, even trivial stimulation set off active episodes which led to progressive proliferation and distortion of skin and heart valve, respectively.

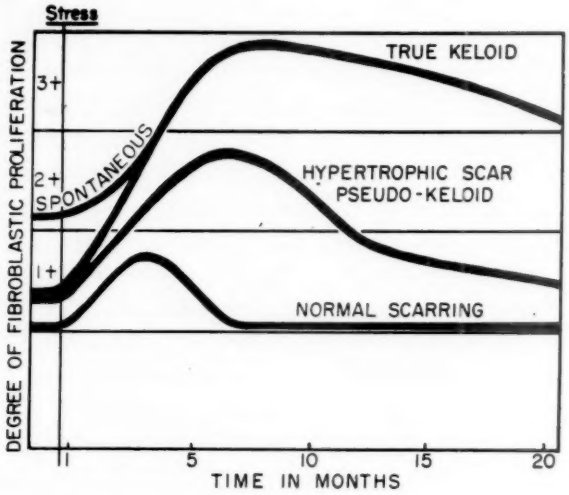

Fig. 1.

The information which has been accumulated leads to extension of present working hypothesis to include, for practical purposes, the concept that heparin may be the usual natural inhibitor of fibroplastic proliferation under normal conditions. The initial hypothesis (regarding rheumatic states) held that there is a lack of adequate available heparin at sites of tissue damage.[38] In the current instance of keloid formation the balance between the unknown stimulator of wound repair and the inhibitory heparin appears to be upset when heparin is abnormally tolerated, bound, neutralized, or destroyed. Activity is phasic; it is likely related to stress at the time of the initial injury and is subsequently followed by complicated changes. Isolated laboratory findings must be correlated with the clinical stage and condition of the patient.

CLINICAL PATTERN

The normal late sequence of events in wound repair is as follows (see Fig. 1): The clean, rapidly healed wound without physical stress or inflammatory change gets progressively thicker, red, and indurated in a small zone about its margins

*Department of Microbiology cooperating in large part with Cardiovascular Services in community type study supported in part by the Office of Naval Research and extended to other hospitals in the Greater Kansas City area.

for two or three months, then the healing area begins to soften, becomes more pale, and diminishes in size. The process of regression goes on for from four to six months, but changes very little after that when fibroblastic activity comes back to the initial prewound level. In large open wounds with a prolonged early phase (six to twelve months) there is a greater proliferative activity especially at the margin, but regression usually takes place to the normal basic level in another year or less. The most marked activity is seen in keloid formation with proliferation continuing to greater extent and much longer. Little or no resolution takes place over the ensuing years. In general, the so-called true keloid will not appreciably regress.

No sharp line between true keloid or hypertrophied scar should be drawn, as one is a degree of the other. Although some pathologists believe there is a pathognomonic histologic determination, in these studies distinction is not so sharp. The factor of time is intimately related to the scar-keloid designation. A proliferative wound reaction that might be called a keloid at one time would be definitely only scar some months or years later. The extent of causative injury is, also, a matter of degree but, in general, the slight local wound that develops massive proliferative change is more truly keloid; the great hypertrophic scars following severe burns seem more likely induced by changes related to stress. Such keloidlike scars are much more prone to regress. An exact designation has been difficult and, therefore, the terms keloid or hypertrophied scar have been loosely used to connote the same progress, differing in degree and related by time to the injury.

METHODS AND MATERIALS

Because, as a reliable source of hypertrophic scars or keloids, little is known about animals (with the possible exception of monkeys[5] and horses[39]), with reference also to dogs and cattle, studies on human beings were employed (Table I).

TABLE I. CLASSIFICATION ACCORDING TO CLINIAL STATUS AT TIME OF LABORATORY STUDY

SYMBOL	TYPE	NUMBER OF CASES
+++	True Keloids (K)	5
++	Hypertrophied Scar; (Pseudo-keloids) (HK)	16
+	Scar (Rapid resolution) (S)	7
O	Minimal Scar (O)	4
B	Open Burns (B)	9
		41

In the over-all study of forty-eight cases including some patients whose blood, dermis, or scar were used in earlier tissue culture experiments, thirty-two patients with scars and keloids and nine patients with acute burns were studied by heparin tolerance and diphenylamine determination. These patients are classified and analyzed clinically according to the data in Tables I and II. Only one of the four hypertrophied scar patients was above 40 years of age, all the keloid, hypertrophied scar patients were below 40 years of age.

TABLE II. CLINICAL ANALYSIS OF CASES OF KELOIDS, SCARS, AND BURNS, WITH HEPARIN AND DIPHENYLAMINE STUDIES

	TYPE OF INJURY		AGE IN YEARS				SEX		RACE	
	BURN	OTHER	<10	10 TO 20	20 TO 40	>40>	M	F	WHITE	NEGRO
Scars or keloids	26	6	11	5	12	4	16	16	18	14
Open burns	9	0	0	3	4	2	7	2	7	2

It should be noted that there is a high preponderance of Negro to white patients in this series (out of proportion to the racial ratio seen in this medical center). Of the five designated true keloids, four were in Negro women between the ages of 20 and 40 years. Minor trauma was the cited cause in these four; the other one occurred in a 27-year-old white woman who had been severely burned. Nearly all hypertrophic scar patients occurred as the result of burns.

HEPARIN TOLERANCE STUDIES

Hypercoagulability of the blood is depicted in tests for increased tolerance to heparin. Information may be obtained by testing for delay in blood coagulation time in vivo by response of patient to injection, or in vitro to the addition of heparin of freshly drawn blood. We are employing a modification of in vitro test for clotting time and measuring clot delay which is the difference between the coagulation time of blood treated with heparin and that of untreated blood. In vitro tests usually involve tube dilutions;[40] however, in our studies, a simplified test[37] used for studies on rheumatic fever has been employed. A prolonged heparin tolerance test is probably of no well-defined significance.

In current studies of over 400 persons involving over 900 determinations, the mean clot delay is between nineteen and twenty-one minutes. Increase in heparin tolerance is definite at delay of only ten minutes or less with a border line between ten and one-half and eleven and one-half minutes. Control series of 161 individuals include three categories, viz., normal, postoperative, and miscellaneous disease. An increased heparin tolerance of 3 per cent incidence was found in the miscellaneous disease, but there have been none in the normal group. Highest proportion is 10 per cent in the postoperative cases.

The greatest increase in heparin tolerance was found in severe burns during the acute phase. Eleven of the sixteen determinations in severe burns (over 20 per cent of the third degree burns still open) were above the mean, and seven of these were well within (abnormal) increased zone. None of the minor burns showed increased values. All determinations on the open burns were made early in the first three months. The most striking abnormal values were quite early and in the severe burns.

Keloids, hypertrophic scars, and simple scars were studied in the phases of Healing (II) and Resolution (III). The initial reactive phase I (first sixty days) can be defined arbitrarily as in Fig. 2. This phase means the period from time of injury until fairly complete wound coverage. The healing phase II is that time chosen roughly for the period from two to six months, during which healing is likely to appear hypertrophic. Some determinations were made when the time of injury could not be well determined, especially as in true keloid

formers (well after the third phase, as shown in Fig. 2). High values are found in the keloid patients, with all except one determination being in the increased zone. Two more recent determinations are in patients with quite inactive old keloids, and they have given isolated low values. Trivial injury occurred over three and one-half years ago, in fact, in one patient it has been nineteen and one-half years since the active keloid formation. Only four of the twenty-nine determinations made in cases of scars were in the pathologic zone; however, all of these were less than eight months after injury. These were in four patients who were believed at first to be keloid formers. In general, the late determinations (after the first year) of heparin tolerance studies were well within the normal zone. All of the simple scar formers with but little fibroblastic reaction showed values within the normal range.

The most striking feature is that these late cases would not be confused with individuals in the control group. Abnormal values in postoperative series were in early patients who may be prone to thrombotic complications. In the laboratory it was surprising to observe increased heparin tolerance in a normal-appearing outpatient.

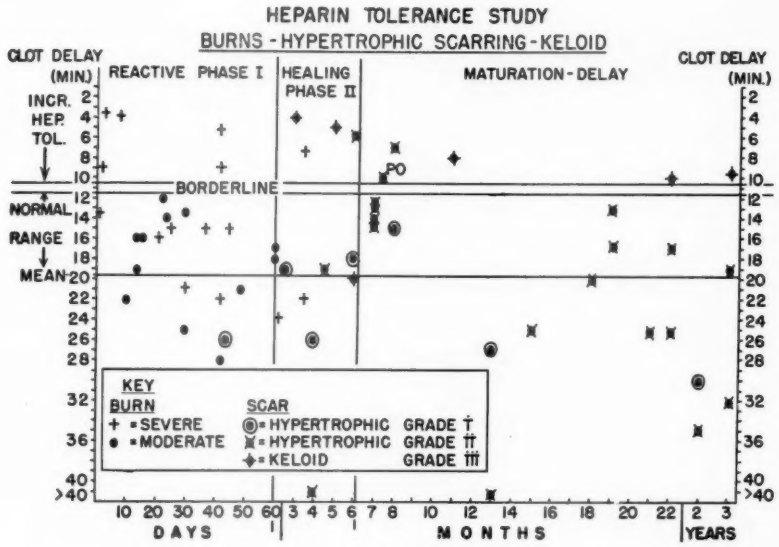

Fig. 2.

DIPHENYLAMINE PURPLE REACTION

Diphenylamine purple reaction is employed to depict cellular activity and it is believed to reflect a relative level of circulating polysaccharide. It had been initially employed in testing for malignancy.[41] This curious reaction is currently the subject of considerable investigation regarding mucoproteins of lymphoid tissue, and study was also carried out with relating determinations in serum to certain disease processes.[42]

We have been using relative levels applying these as reference points of activity. We have evaluated the normal range at ±11 per cent of normal pool. For each of these tests which require meticulous care, determination of dupli-

cate samples are compared with spectrophotometric readings of pooled control blood in duplicate in the same water bath. The relative levels of activity have been set arbitrarily to correspond with means of +62 per cent for marked activity and +42 per cent for moderate activity with reference to the studies just cited.[43]

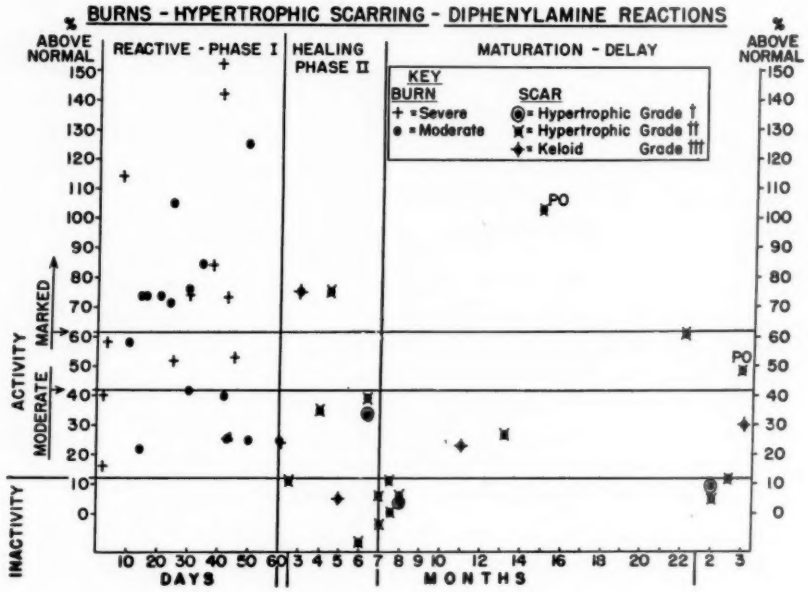

Fig. 3.

In the present study of thirty-two burns and keloids, the accumulated experience contributing to this analysis involved over 400 persons and approximately 2,000 diphenylamine determinations. In the control group of persons the medium value for normals was –3 per cent and that for miscellaneous diseases was +27 per cent. Following injury or major surgical procedures the peak elevation is not reached until after the third day, and the median figure is well up in the zone of marked activity. Current findings in cases of hypertrophied scars and keloids of moderate to marked activity in the second and third phase

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Fig. 4.—Photomicrographs of scars and keloids in different phases of activity.

A, B. Y., a 9-month-old white male infant, had a healed hypertrophic scar on the back of the hand. He was burned at the age of three months. Note marked cellular activity of inflammatory reaction in dermal area. Magnification, ×90. Stain, hematoxylin and eosin.

B, I. J., a 17-year-old Negro girl, had an inactive old burn scar on the leg. Note dense matting of collagen fibers with almost no cellular elements except in small intact blood vessel. Magnification, ×90. Stain, hematoxylin and eosin.

C, C. P., a 5-year-old white female child, had a hypertrophic scar on the back of the hand, burned two years before. The case was similar to that in *A* (higher magnification). Note degranulating tissue mast cells with exposed swollen nucleus and linear chromatin (Anitschkow type of arrangement) immediately beneath epithelium of upper left area. Magnification, ×382. Stain, Wright's method.

D, R. M., a 28-year-old Negro woman, had a keloid still in very active stage developed in the lobe of the ear following piercing. Note proliferation of large immature cells between broad collagen bundles. Compare with *B* (at same magnification). Magnification, ×90. Stain, hematoxylin and eosin.

E, R. M. (same patient as *D*). Photomicrograph of area from center of active keloid. Note single degranulating mast cell among large immature fibroblasts. Magnification, ×382. Stain, alcoholic toluidine blue solution.

F, R. M. (same patient as *D*). Photomicrograph of skin area adjacent to active keloid, showing many typical highly granular tissue mast cells with deeply metachromatic staining. Magnification ×382. Stain, alcoholic toluidine blue solution.

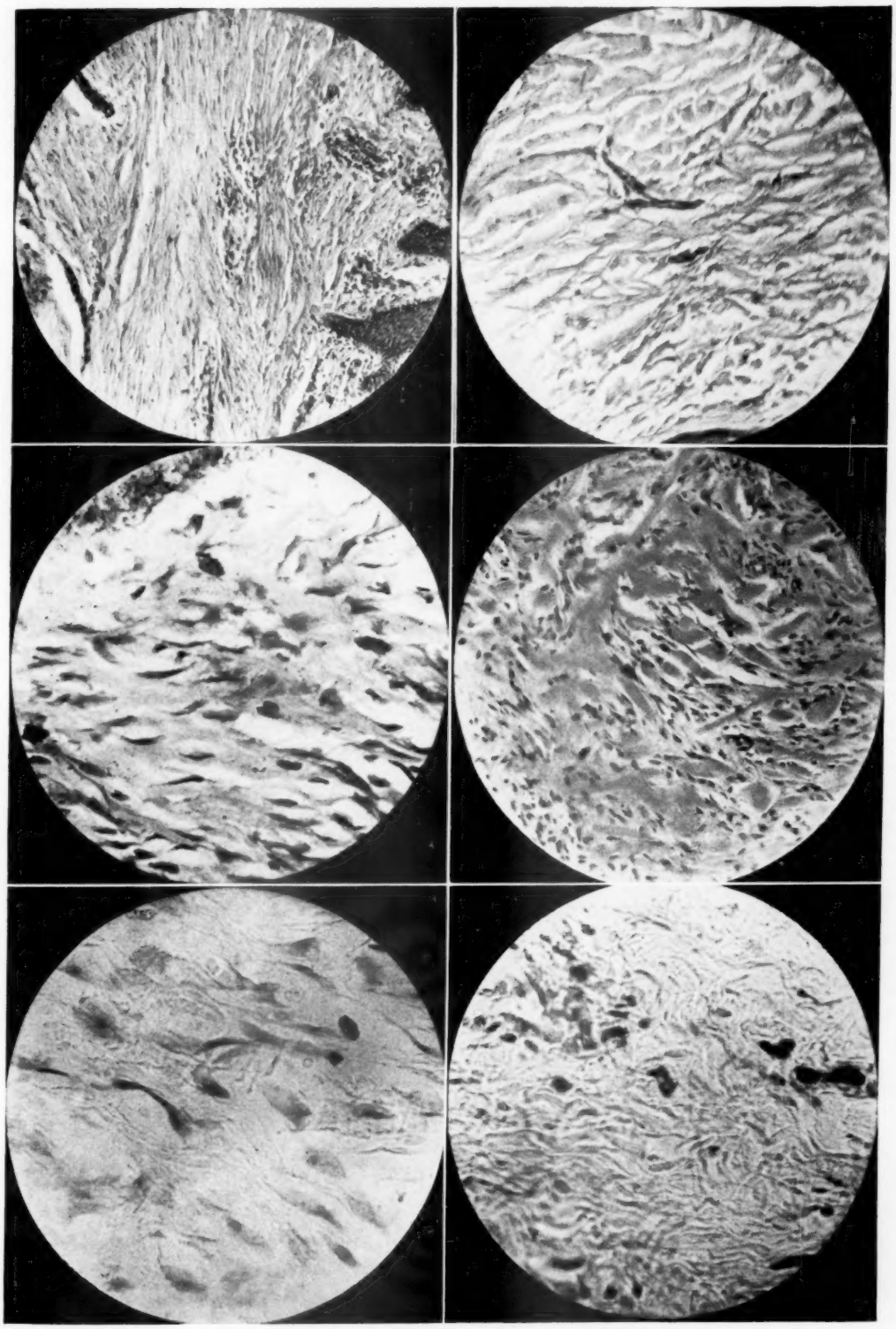

Fig. 4. *(For legend see opposite page.)*

of their course have significance in the concept of the pattern of response with proliferation of tissue.

HISTOPATHOLOGY

The status of tissue mast cells is being studied in cases of burns, hypertrophic scars, and keloids. This is in an attempt to throw additional light upon the role of heparin in proliferative reactions of mesenchymal tissues.

Our findings in the first seventeen cases agree essentially with an earlier observation,[14] especially with reference to keloids. This observation focuses attention upon degranulation of mast cells as an important feature actually within an area of progressive cellular proliferation of the keloid in which large immature fibroblasts are prominent. In the degranulating cells the nuclei appear larger and somewhat vesicular instead of being crowded into small indistinct forms by the densely packed and more coarse cytoplasmic granules of the typical tissue mast cells (see Fig. 4, *E*). Typical mast cells (see Fig. 4, *F*) appear numerous at the periphery of the keloid lesions as well as in the adjacent area of skin; this is in contrast to the small numbers of mast cells within the lesions.

Nuclear changes in degranulating tissue mast cells was pointed out in work from which this present over-all project stemmed.[43] The linear bar of chromatin, characteristic of the Anitschkow type of cell, was identified in tissue mast cells, and this appears incident to degranulation of typical metachromatic granules. Such nuclear changes in cardiac mast cells were cited[38] as having occurred in considerable numbers in Streptococcus-infected monkeys which had been injected with toluidine blue and protamine to exhaust endogenous heparins. In Fig. 4, *A* is presented marked inflammatory reaction in a case of hypertrophic scar; a degranulating tissue mast cell with bar type of nuclear change is illustrated just beneath the epithelium (Fig. 4, *C*) in a similar case. Proliferation of fibroblasts is much less intense in the instance of this lesion than in the true keloid illustrated in Fig. 4, *D*, but, upon study of higher magnification of the same keloid section, the nuclear material in the degranulating mast cell shown in Fig. 4, *E* appears somewhat linear. Neither proliferative nor inflammatory cellular reaction is observed in case of the well-healed old scar which is the source of Fig. 4, *B*.

DISCUSSION

Prominence of tissue mast cells in the skin some distance from the immediate margin of keloid lesions may be considered consistent with systemic compensatory reaction. The evidence of systemic effects has been greater than had been anticipated at the outset of this study; this accounts for the emphasis upon increased heparin tolerance. The phase of the problem which deals with hypertrophic scars or pseudokeloids is interpreted as reflection of local injury and systemic stress, especially in a group of young persons. In the long-range program, comparative study of age and species deals with skin and cardiac tissues under conditions which will require interpretation of the role of infection. This centers attention upon staphylococcal infection (by *Micrococcus aureus* with prominent drug resistance)[44] in skin and upon streptococcal infection in cardiovascular tissue. One of our most striking keloid formers was a

patient whose worst lesion was at the site of trauma incident to chicken pox. She also had a past history of active episodes of rheumatic state.

Degranulation of tissue mast cells has followed experimental infection[38-45] in the early acute phase. The role of heparin[46-48] has been under investigation and is being studied in another portion of this project.[49] That portion which deals with mast cell changes and antiheparins by experimental approach will appear in more detailed analysis elsewhere. The occurrence of extracardiac Anitschkow cells has been described,[50] but this is the first report which we have encountered of this type of cell in the skin or of significance attached to it in proliferative reactions in dermal tissue.

Evidence is developing which seems to indicate that inhibitory factors may be relatively exhausted, bound, or destroyed, and the relationship of heparin in this respect appears significant. Fundamental cellular and chemical changes appear to be reflected at the human end of the spectrum in comparative biology as we study increase in tolerance to heparin and attempt to relate cytologic changes in tissue mast cells to such physiologic alterations.

SUMMARY

1. Evidence is presented in support of an hypothesis that proliferative fibroplasia is phasic as related to reaction to injury, repair, and degree of maturation in the reparative process.

2. Clinical data of a series of burns, hypertrophic scars, and keloids are presented.

3. A tendency toward increased heparin tolerance is noted in the early phase of burns; it is still increased later in keloid formation.

4. Diphenylamine determinations on blood of these patients have a similar, although less striking, tendency to parallel fibroblastic activity.

5. Correlation between status of tissue mast cells and the degree of cellular activity of fibroblasts is observed.

The authors express their appreciation to John Howieson, Lorene van der Smissen, and Wilda Werner for technical assistance in certain phases of this program.

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DISCUSSION

DR. J. GARROTT ALLEN (Chicago, Ill.).—First of all, I want to congratulate Dr. Robinson and his group on this very stimulating study and excellent preservation.

I think it is a fair statement to say that we do not know what the normal function of heparin is. It is, of course, an antagonist of coagulation, but that seems to be incidental.

Dr. Robinson alluded to heparin in radiation. We were convinced that we had found heparin in total body radiation in the blood of dogs. For three years we were able to find evidence of that, and for five years we have not been able to find it. There are many reasons why the differences in our own experience cannot be explained at this time.

There is another point regarding the dye staining with toluidine blue that might be of interest. This relates to an observation by Penny and Balfour. As I recall their observations, the ascorbic acid content of animal tissue and adrenal function had a direct relationship to the staining capacity of toluidine blue. The azurelike appearance of tissue which the histochemists attributed specific for heparin has proved erroneous, just as Dr. Robinson has stated. This claim led us and others to assume that this is a specific heparin reaction. Such is not the case.

The last point that I would like to make is that heparin almost surely is not free in the blood. It has never been found with certainty in normal blood. It has been found only in extreme conditions of anaphylaxis where it persists but a short time. It is bound by a number of proteins, especially the basic ones, and behaves according to the law of mass action. If it is normally present in blood, it is probably bound.

DR. ROBINSON (Closing).—The studies of Penny and Balfour alluded to by Dr. Allen are quite correct, and you will note that in this discussion I have omitted the mention of many substances which may have to do with the basic mechanism of the repair of wounds. I have left out all statement about hyaluronic and hyaluronidase and some of the basic chemistry of the nucleic acids and vitamin C. It is true that this information appears in the literature. Some of the investigators at present are so confused that they don't know where they stand themselves; and I will assure you gentlemen that if you peruse the literature, unless your mind is very keen, you, too, will become a bit confused, by differences in terminology and differences in ideology. However, we promote this study, and I hate to use the word "promote," stating only that heparin may be the important key of the inhibitor mechanism. There is no proof for heparin. At present, work is under way to try to elucidate heparinases to the point that they can be shown histochemically. To try to interpret what happens from histochemical analyses may never be entirely accurate. It is only relatively accurate.

RELATIONSHIP OF SONICALLY DISRUPTED PLATELETS TO SERUM VASOCONSTRICTOR ACTIVITY

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SPONTANEOUS hemostasis is of importance to surgeons and it is generally agreed that blood platelets play a significant role in this physiologic process. Currently, most workers in the field of coagulation and hemostasis are of the opinion that platelets participate in three distinct ways in aiding in the arrest of hemorrhage. First, in so far as actual clotting is concerned, it is held by various investigators that platelets provide substances necessary for the initiation,[1-3] propagation,[4] and retraction[5] of the clot. Second, platelets coalesce within the lumina of small transected vessels and these aggregates occlude the defect producing cessation of bleeding.[6] Third, there is evidence to suggest that platelets, in conjunction with a plasma factor, are instrumental in the elaboration of a vasoconstrictor substance or substances present in serum. These substances may conceivably aid in retarding bleeding, but opinions are at variance. It is with this last function that the experimental work herein reported concerns itself.

It has been known for many years that serum contains pharmacologically active substances which stimulate smooth muscle contraction. O'Conner, one of the earliest workers, recognized that these substances were formed during the clotting process. Subsequent investigators compiled considerable evidence suggesting that the disintegration of platelets was necessary to the formation of these vasoconstrictor substances.[7-10] It remained, then, to determine whether or not the vasoconstrictor substance existed in an active, preformed state within the platelets or whether it required an activator present in plasma. The reverse possibility must also be considered, namely, that the platelets contain an activator of a plasma vasoconstrictor precursor. The work of Reid[7] and, more recently, Zucker[10] indicates that although the clotting process is noted to release vasoconstrictor substances, presumably from platelets, it is possible also to demonstrate active vasoconstrictor properties in washed, lysed platelet suspensions. However, much of the evidence is indirect; therefore, with improved techniques of platelet separation and the application of ultrasonic vibration as a means of fragmenting cells, we undertook to re-examine the concept that platelets contain active preformed vasoconstrictor substances.

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METHOD

Platelet Collection.—All glassware used in the collection of platelets was siliconated, and differential centrifugation was carried out in a refrigerated centrifuge at 10° C. in Lusteroid tubes. Whole blood from blood bank donors was filtered through approximately 75 Gm. of the cation exchange resin, Dowex-50.[11] The ion exchange resin was held in a metal container which was interposed between the donor and the collecting ACD-1 bottle (Fig. 1). Prior to filtration of the blood, the resin was washed with distilled water and saturated with normal saline solution. The metal container with the resin was then autoclaved and the apparatus was assembled. Through the resin was passed 500 c.c. of whole blood. The metal container was then removed and the resin placed in a chilled beaker containing 200 c.c. of modified human globin solution.* The globin solution was prepared by dissolving 16 Gm. of dry globin

Fig. 1.—Metal container holding the ion exchange resin shown in proper position above the collecting bottle.

in 200 c.c. of normal saline solution. The resin and globin were thoroughly mixed to elute the platelets from the resin, and the resin was then allowed to gravitate to the bottom of the container. The supernatant solution, containing the platelets and other formed blood elements, was placed in a glass separatory funnel and allowed to stand at room temperature for two hours. The sedimented

*Supplied by The Upjohn Company.

red and white cells were drawn off and the supernatant fluid was placed in Lusteroid tubes and centrifuged at 2,000 revolutions per minute for twenty minutes. All but approximately 5 c.c. of the supernatant fluid was decanted and discarded. The sediment was resuspended in the remaining 5 c.c. of solution by shaking. The suspension was then centrifuged at 2,500 revolutions per minute for ten minutes to concentrate the platelets. The supernatant fluid was discarded and the concentrated platelets were resuspended in 50 c.c. of normal saline solution. This washing process was repeated three times. The final sediment was then suspended in 5 c.c. of normal saline solution and was centrifuged slowly at 700 revolutions per minute for five minutes for the purpose of throwing down any remaining red blood cells. The supernatant saline solution, containing the platelets, was removed and platelet counts were performed on the suspension using the Rees-Ecker method and diluting fluid.

Ultrasonic Disintegration of Platelets.—The platelets were fractured by exposure to ultrasonic vibration. We placed 10 c.c. of the platelet suspension in a water-cooled oscillation chamber of a 200 watt, 10 kilocycle Raytheon magneto-striction oscillator. The platelet suspension was then exposed to ultrasonic vibration for ten minutes with the oscillator performing at maximum capacity. Platelet counts were made on the suspension before and after ultrasonic exposure. The disintegrated platelet suspension was then tested for vasoconstrictor activity by rabbit-ear perfusion technique.

Vasoconstrictor Assay.—The vasoconstrictor properties of serum and disintegrated platelets were determined by the rabbit-ear perfusion technique of Page[12, 13] with minor modifications. Flemish giant rabbits weighing not less than ten pounds were anesthetized with intraperitoneal Nembutal. The central artery of the ear was dissected free in situ and the ear was then severed near the base. A glass cannula was introduced into the previously dissected artery and perfused with 50 c.c. of perfusion fluid to insure patency of the system. The ear was then mounted in the perfusion chamber and the perfusion was started. A modified Locke-Ringer* solution, which was prepared just prior to the beginning of the experiment, was used as the perfusate. The mean pulsatile perfusing pressure was maintained at 20 mm. Hg throughout each experiment. The temperature within the perfusing chamber was maintained at 37° C. by a thermoregulator described by Page. The test materials were not introduced into the perfusion system until the drop rate of 100 per minute or more was obtained. Drop rates were determined by counting with a stop watch at minute intervals. Following a control period during which the drop rate was stabilized, aliquots of 0.2 ml. and 1 ml. of the assay material were injected into the perfusing system with a tuberculin syringe using a No. 26 needle. Diluted serum (1:1 with normal saline solution) from normotensive blood donors, sonically disrupted platelets from the same person, and saline solution were assayed on one ear and constituted a single experiment. The test material was placed in the perfusion chamber several minutes before injection to allow it to reach the temperature within the perfusion chamber. The drop rate was

*NaCl, 9.00 Gm., KCl, 0.41 Gm., $MgCl_2$, 0.06 Gm., $NaHCO_3$, 0.50 Gm., dextrose, 0.50 Gm., 1 L. distilled water.

determined at thirty-second, and one-, three-, and five-minute intervals following injection. In instances where vasoconstrictor activity was noted, the drop rate was allowed to return to control levels before further assays were performed.

RESULTS

Relatively pure suspensions of concentrated platelets were prepared from whole blood by filtration through a cation exchange resin, by increasing red blood cell sedimentation with a globin hydrophilic colloid, and by differential centrifugation. By combining these three methods, 10 c.c. suspensions of intact platelets with counts of 205,000 to 330,000 per cubic millimeter were obtained. The normal morphology of the platelets did not appear to be disturbed, and very little clumping was observed. Only rare red blood cells were noted on microscopic examination of the platelet suspensions.

These platelets were then subjected to ultrasonic vibrations and were successfully disintegrated as evidenced by a marked decrease in the platelet count of the suspension following oscillation (Table I). No attempt was made to achieve disruption of all platelets by continuing the ultrasonic vibration longer than the arbitrarily selected ten-minute interval.

TABLE I. PLATELET COUNT (REES-ECKER)

EXPERIMENT	PRESONIC	POSTSONIC
1	330,000	55,000
2	270,000	10,000
3	220,000	40,000
4	230,000	50,000
5	205,000	60,000
6	215,000	55,000

The suspension of disrupted platelets, when assayed for vasoconstrictor activity, showed no appreciable effect on the drop rate of a perfused rabbit ear when aliquots of 0.2 ml. (Figs. 2 to 5) and 1 ml. (Figs. 6 to 9) were used. A total of eight such experiments was performed with consistent findings. Vasoconstrictor activity of a marked degree was demonstrated in 0.2 ml. of serum, as evidenced by a prompt fall in the drop rate following injection with a gradual recovery to control drop rate levels within five to seven minutes (Figs. 2 to 5). Increased vasoconstrictor activity was noted when 1 ml. of serum was employed (Figs. 6 to 9). This vasoconstrictor effect was not altered when the serum was subjected to ultrasonic oscillation. The saline solution was without effect.

DISCUSSION

The data obtained from these experiments would indicate that platelets do not contain an active preformed vasoconstrictor agent which is liberated by mechanical lysing. The evidence in favor of such a principle in platelets, mentioned earlier in this paper, might be explained by the presence of plasmatic factors contaminating the previous platelet preparations studied.

It is fairly well established that the clotting process releases an active vasoconstrictor demonstrable in the resultant serum, which is also present to a lesser

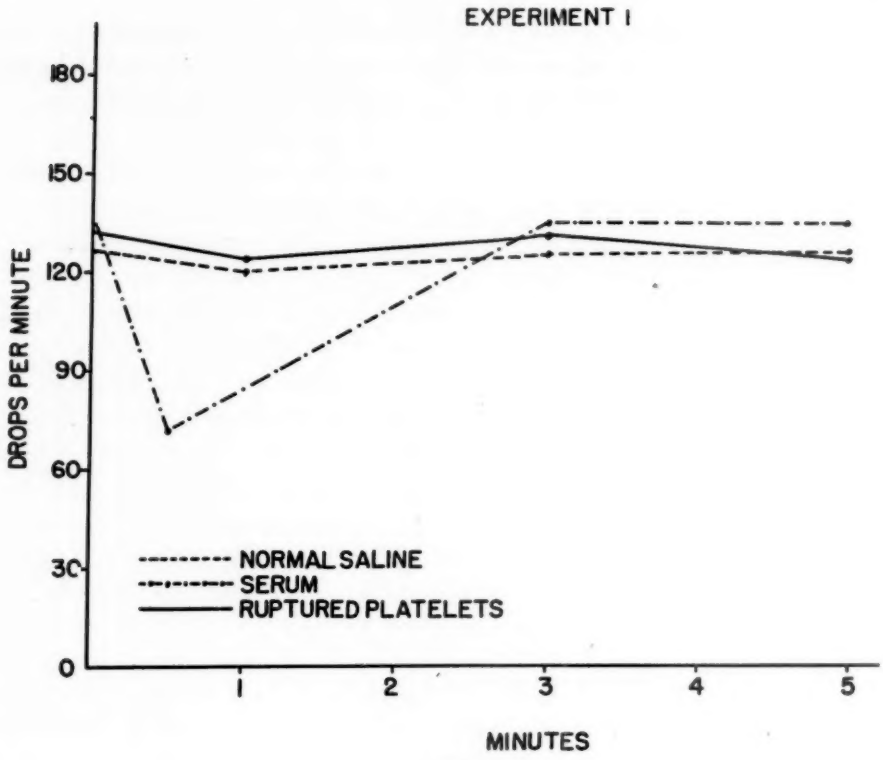
EXPERIMENT I
DROPS PER MINUTE
180
150
120
90
60
30
0
1
2
3
4
5
MINUTES
NORMAL SALINE
SERUM
RUPTURED PLATELETS

Fig. 2.

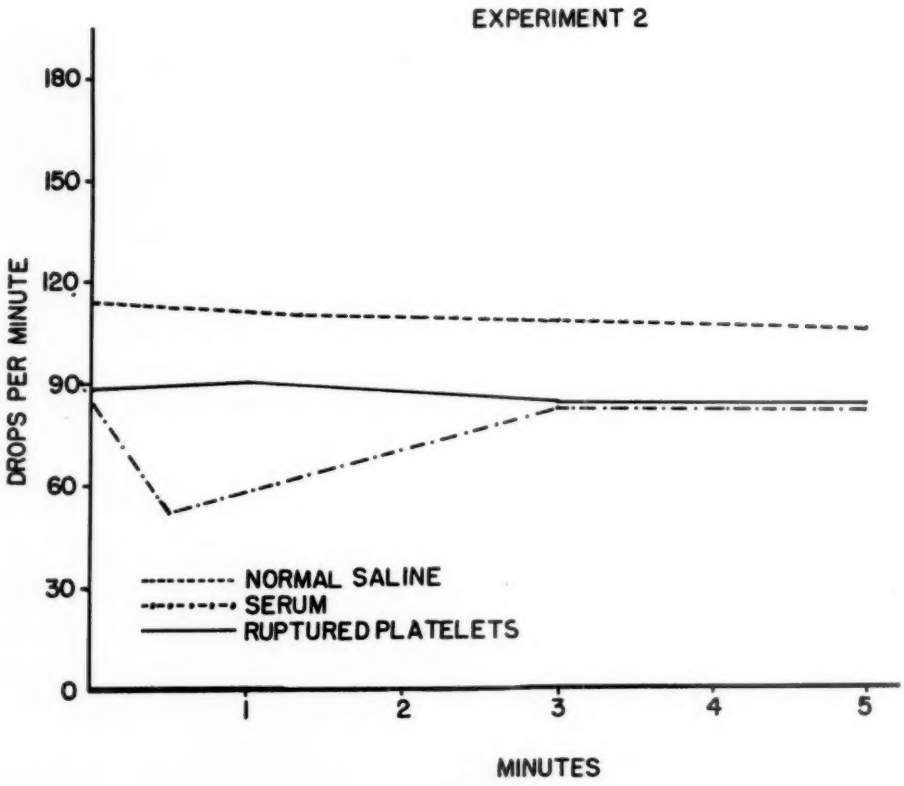
EXPERIMENT 2
DROPS PER MINUTE
180
150
120
90
60
30
0
1
2
3
4
5
MINUTES
NORMAL SALINE
SERUM
RUPTURED PLATELETS

Fig. 3.

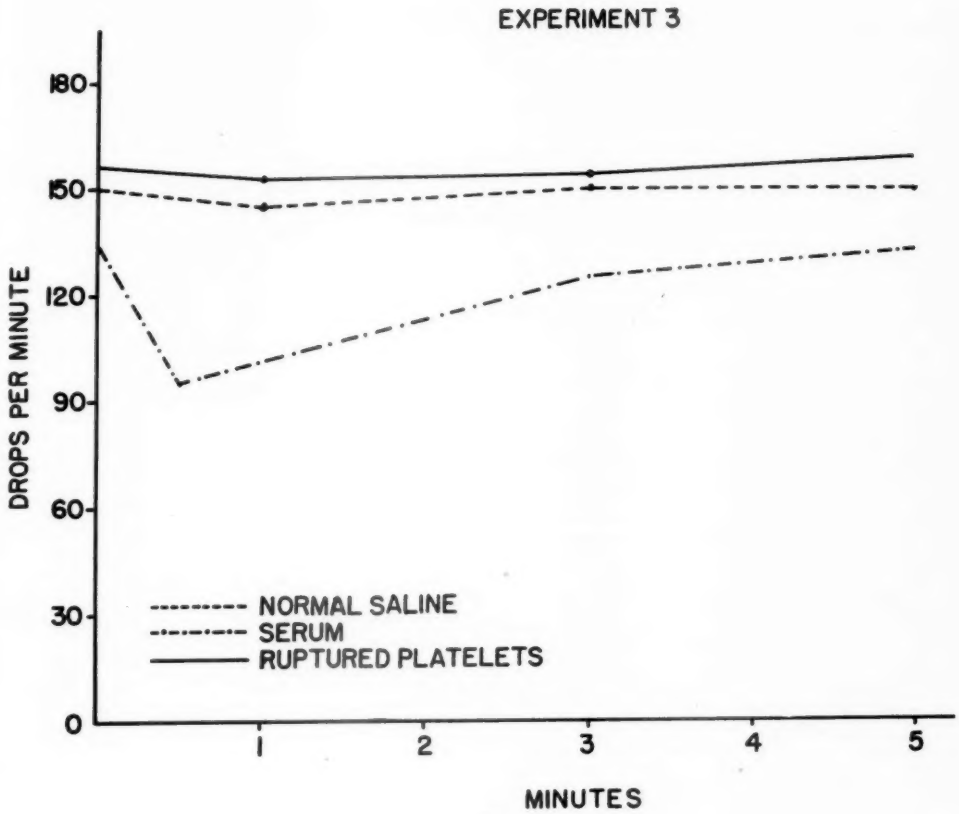
EXPERIMENT 3
180
150
120
90
60
30
0
DROPS PER MINUTE
NORMAL SALINE
SERUM
RUPTURED PLATELETS
1
2
3
4
5
MINUTES

Fig. 4.

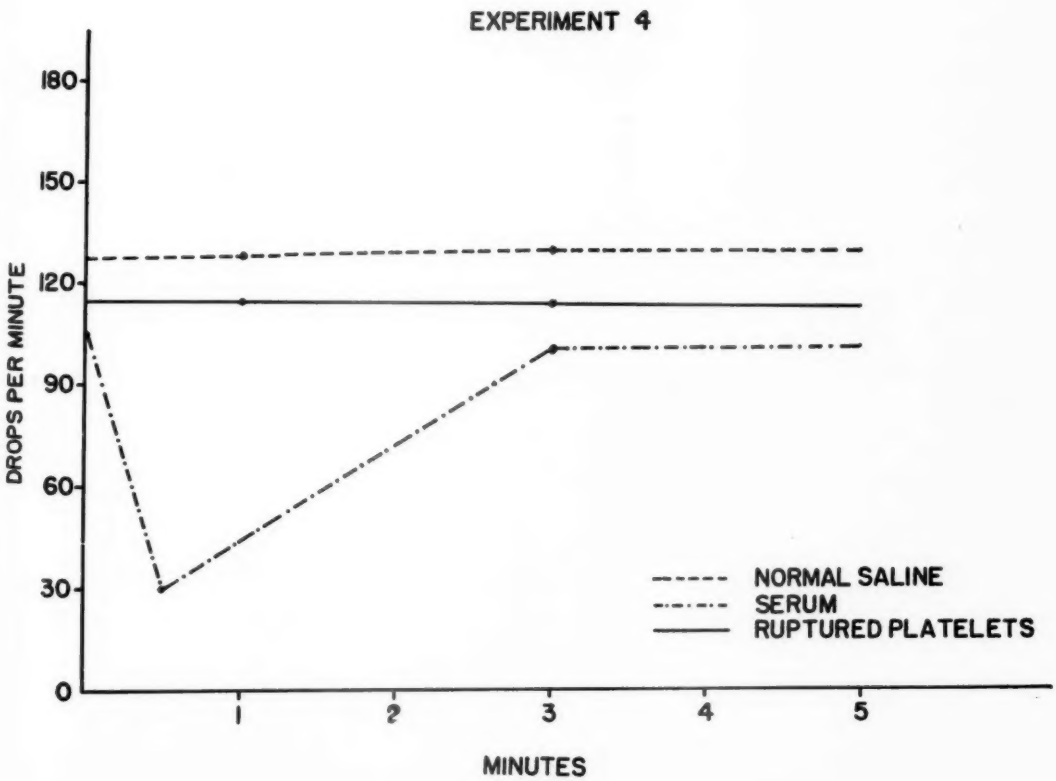
EXPERIMENT 4
180
150
120
90
60
30
0
DROPS PER MINUTE
NORMAL SALINE
SERUM
RUPTURED PLATELETS
1
2
3
4
5
MINUTES

Fig. 5.

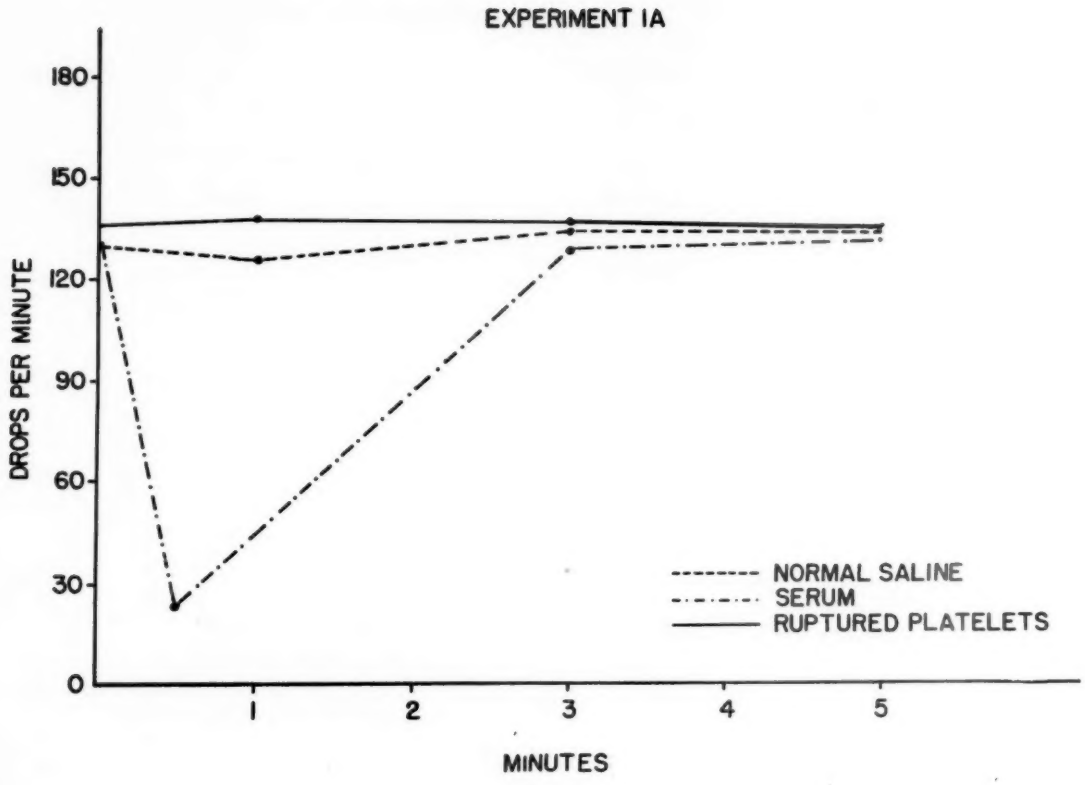
EXPERIMENT IA
DROPS PER MINUTE
180
150
120
90
60
30
0
1
2
3
4
5
MINUTES
NORMAL SALINE
SERUM
RUPTURED PLATELETS

Fig. 6.

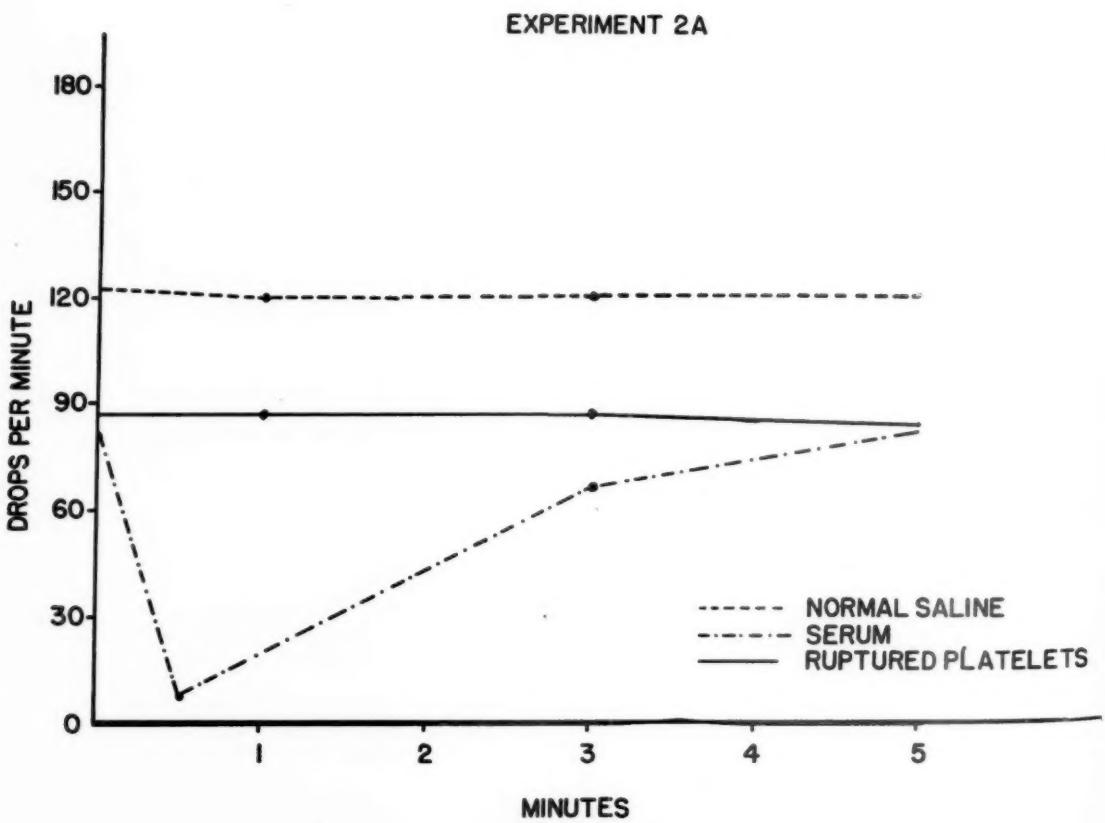
EXPERIMENT 2A
DROPS PER MINUTE
180
150
120
90
60
30
0
1
2
3
4
5
MINUTES
NORMAL SALINE
SERUM
RUPTURED PLATELETS

Fig. 7.

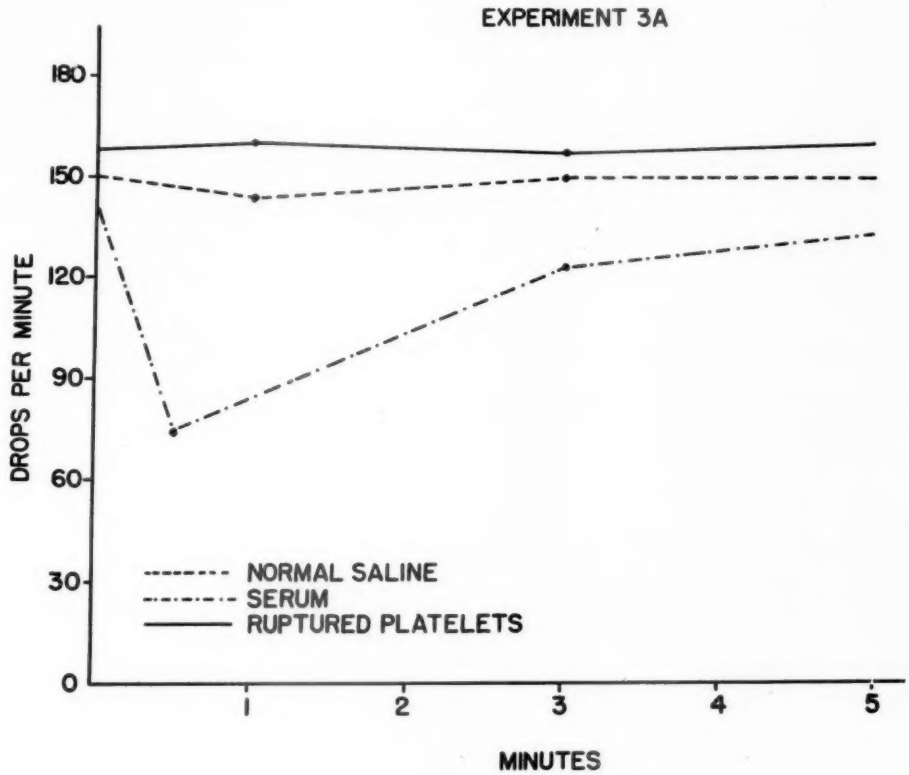
EXPERIMENT 3A
180
150
120
90
60
30
0
DROPS PER MINUTE
NORMAL SALINE
SERUM
RUPTURED PLATELETS
1
2
3
4
5
MINUTES

Fig. 8.

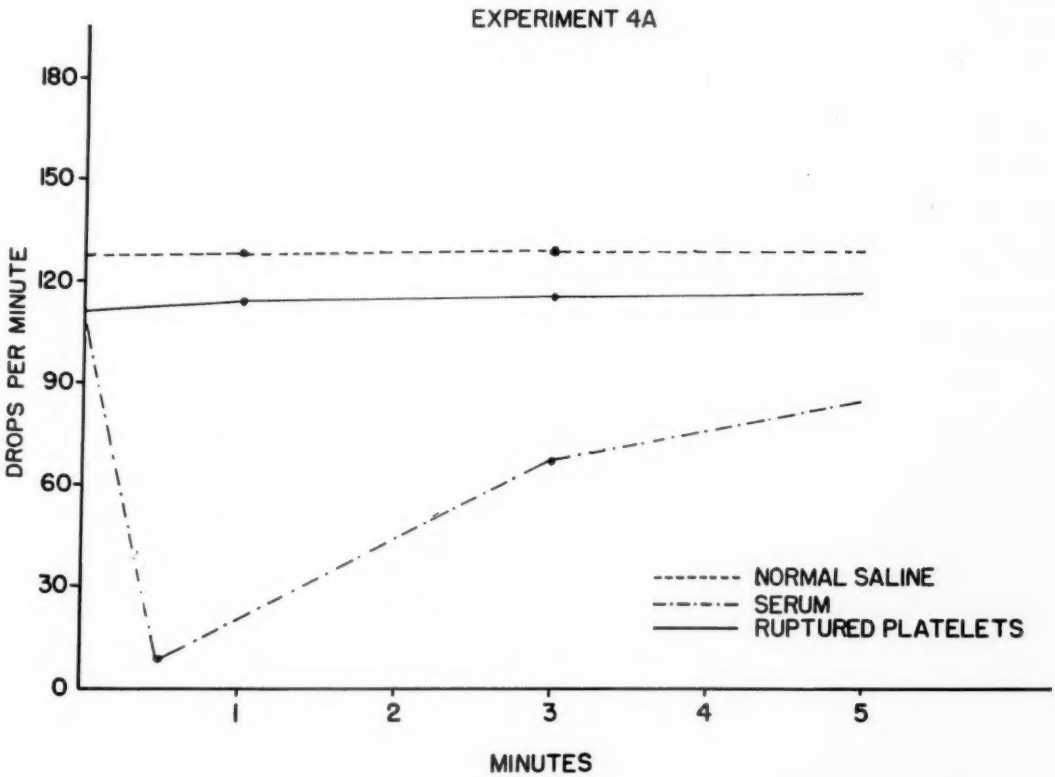
EXPERIMENT 4A
180
150
120
90
60
30
0
DROPS PER MINUTE
NORMAL SALINE
SERUM
RUPTURED PLATELETS
1
2
3
4
5
MINUTES

Fig. 9.

degree in the plasma. The degree of vasoconstrictor activity is apparently directly related to the number of platelets present, but the mechanism by which the platelets participate in the formation of this vasoconstrictor substance remains obscure.

SUMMARY

1. Platelets, mechanically lysed with ultrasonic vibration, when perfused through a rabbit's ear do not exhibit vasoconstrictor activity.

2. The role of platelets and of the plasmatic factor in the elaboration of vasoconstrictor substance following coagulation is discussed.

3. The functions of platelets in spontaneous hemostasis are reviewed.

Acknowledgment.—We wish to acknowledge the cooperation of Dr. Irvine Page and Dr. Louis Pillemer in these experiments and express our appreciation to Mrs. Eleanor Connor and Mrs. Betty Koelliker for their technical assistance. The Dowex-50 was generously supplied by the Dow Chemical Company.

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DISCUSSION

DR. J. GARROT ALLEN (Chicago, Ill.).—This is another field which we have been interested in, and have some work, in a different method, which I think completely confirms that just presented. It is to this effect: if either thrombin or thromboplastin is injected intravenously into a normal dog at a rate not to exceed about twenty minutes for the entire amount, the animal can be completely defibrinated. There is evidence of serious vasoconstriction during the first few minutes of infusion. If thromboplastin is injected into an irradiated animal, which has very few platelets, the same reaction occurs. If coagulation is inhibited by heparin, there is little or no systemic reaction.

BIO-ELECTRIC PHENOMENA AS ETIOLOGICAL AGENTS IN INTRAVASCULAR THROMBOSIS

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THE studies of the potential differences of normal arterial walls and grafts were part of an integrated investigation of the properties and usefulness of freeze-dried arterial homografts.[1] Normal male mongrel dogs were used in these investigations. Freeze-dried aortic homografts, preserved under a vacuum of less than 200 μ after being lyophilized at temperatures lower than –40° C., were stored for specified periods of time before implantation into the abdominal aorta. After implantation, they were left in situ for periods of time up to two years before the dogs were sacrificed. Only one of seventy-six freeze-dried homografts did not function satisfactorily, while 18 per cent of the fresh aortic grafts serving as controls developed thrombi of various degrees.[1] At the time, no explanation could be offered for this statistically valid difference.

Initially, an attempt was made to determine the normal potential difference of arterial walls. After determining these base line potential differences (P. D.) in acute experiments, it was hoped to correlate healing rates in fresh and freeze-dried vascular grafts with changes in P. D. as determined by long-term measurements.[2] Measurements of potential differences were made by two techniques: first, by measuring the P. D. of the recipient aorta, suture lines, and graft at the time of autopsy after specified intervals of implantation and, second, by measuring the changes in P. D. which occurred from day to day in the individual graft in the living animal. Approximately fourteen freeze-dried and fresh grafts were compared in this fashion for periods of as long as twenty-one days.[2]†

Two different potentiometers and three types of electrodes were used in the course of the experiments. The potentiometers were a manually operated Leeds and Northrup device connected in series to a pH meter to increase its sensitivity and a twin-channel recording Sanborn instrument.

The electrodes used were catheter-calomel cell, platinum, or silver-silver chloride (Fig. 1). In all the successful long-term electrode implantation experiments, small polyethylene catheters filled with saline solution and attached to calomel cells were used.

The opinions or assertions contained herein are the private ones of the writers and are not to be construed as official or as reflecting the views of the Navy Department or the naval service at large.

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†Dogs became conditioned and would lie quietly while measurements were made. Rubber tubes connected the catheter electrodes to calomel cells. The system used 0.1 normal sodium chloride as the electrical conducting solution. The catheters were attached in pairs across the aortic wall. The internal electrode was inserted through a branch into the lumen of the vessel. The external electrode was sutured closely to the adventitia of the vessel.

All three electrode types were used in acute experiments so that measurements employing the various electrodes might act as checks on each other. Often, more than one type was applied in a single experiment.

The manually operated potentiometer was employed when single accurate P. D. measurements were required. The recording instrument provided continuous records of the changes which occurred during the dissection, manipulation, transection, grafting, and purposeful injuring of vessels.

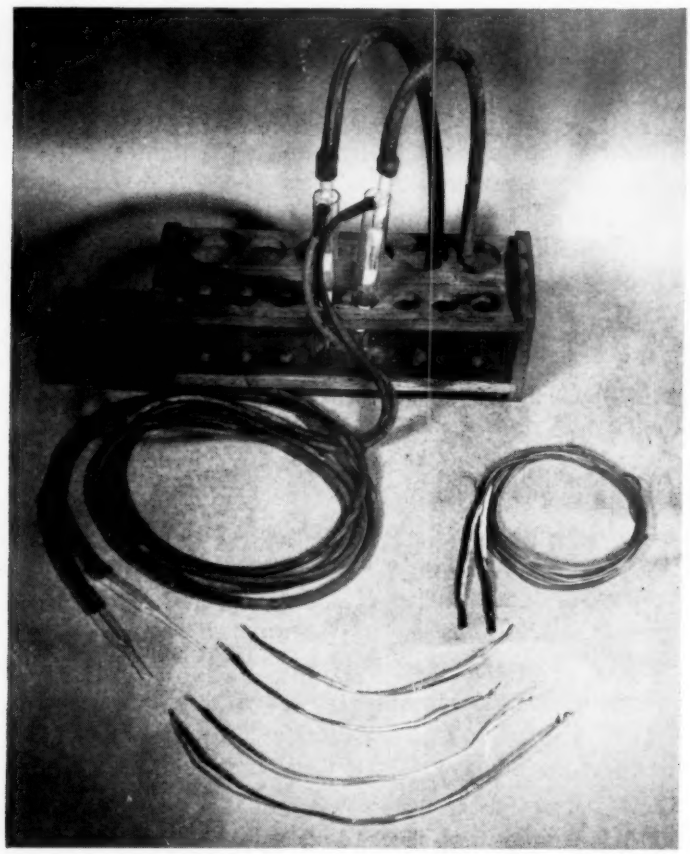
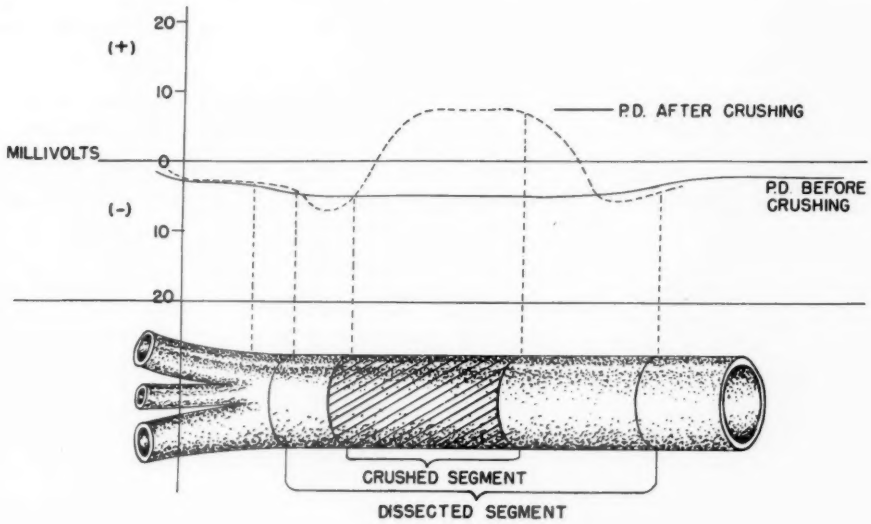


Fig. 1.—Illustration showing the three types of electrodes used in the study: (1) calomel cell electrodes at the top, (2) platinum electrodes with wire leads coiled on the right, and (3) silver-silver chloride electrodes with long polyethylene insulated leads at the bottom.

The experiments to determine the magnitudes and polarity of the normal blood vessel wall demonstrated that its P. D. was in the range of 1 to 5 mv. with the intima negative with respect to the adventitia. The more dissection required to isolate the vessel, the higher was the P. D. within this range (Fig. 2).

Gross injury such as transection, crushing, rough dissection or exposure, and drying usually caused at least local reversal of the P. D. so that the intima became positive to the adventitia.[3] The injury P. D. was in the range of 2 to 5 mv. although it occasionally rose as high as 5 to 10 mv. (Fig. 2). The simplest and least complex forms of vessel injury were transection and simple puncture. Both of these types of injury caused immediate local reversal of the potential in



POTENTIAL DIFFERENCES OF NORMAL DISSECTED ARTERY, SUBSEQUENTLY CRUSHED.

Fig. 2.—Schematic drawing illustrating the increased negativity of the vessel wall P.D. after being dissected from the surrounding tissues, and the reversal of P.D. which occurred after the vessel was crushed.

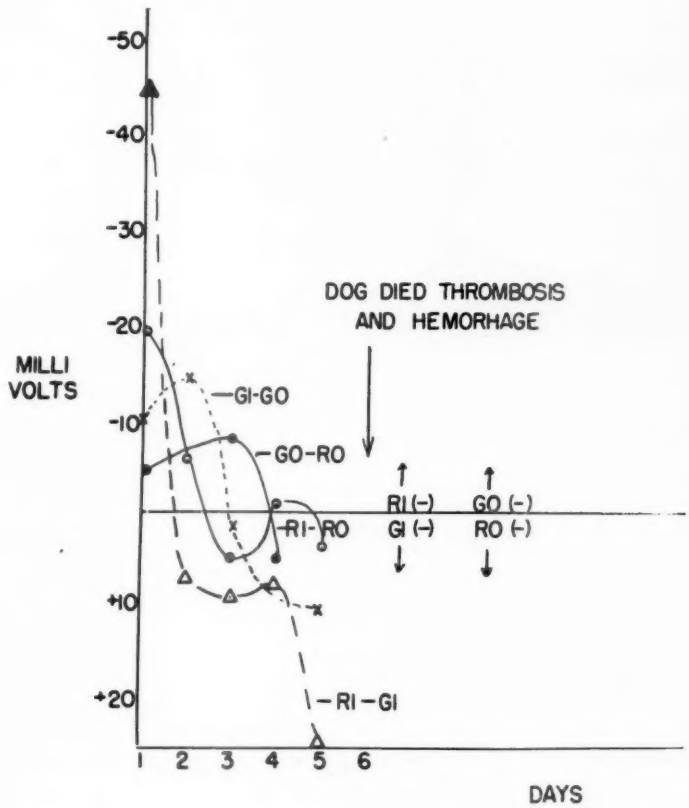


Fig. 3.—Graph of the P.D. of one of the fresh grafts which thrombosed on the fifth day after the P.D. became positive in Experiment 28, April 14, 1952. The P.D. across the graft (*GI-GO*) became positive on the third day. The P.D. across the recipient aorta (*RI-RO*) became positive on the fourth day. The dog developed hindquarter paralysis on the fifth day. At autopsy the graft was grossly occluded.

the aortic wall. The longer the injured segment of vessel, the more complex became the mathematical explanation of the measured injury P. D. This probably was due to volume conduction between the injured and uninjured vessel and between both vessels and the surrounding tissues. Thrombi invariably formed in the grossly damaged segments of the experimental arteries and veins. All freshly removed segments of artery after being exteriorized in saline solution or tissue culture media for thirty to sixty minutes displayed reversal of potential, characteristic of injury. The reversed P. D. may rise as high as + 10 to 12 mv. at the end of four to five hours. This P. D. falls off as the tissue begins to die and is usually near, or at, 0 at the end of twenty-four hours. Usually the injury P. D. present at implantation of fresh vascular tissue disappears, and the tissue reverts to normal polarity during the first postoperative day.

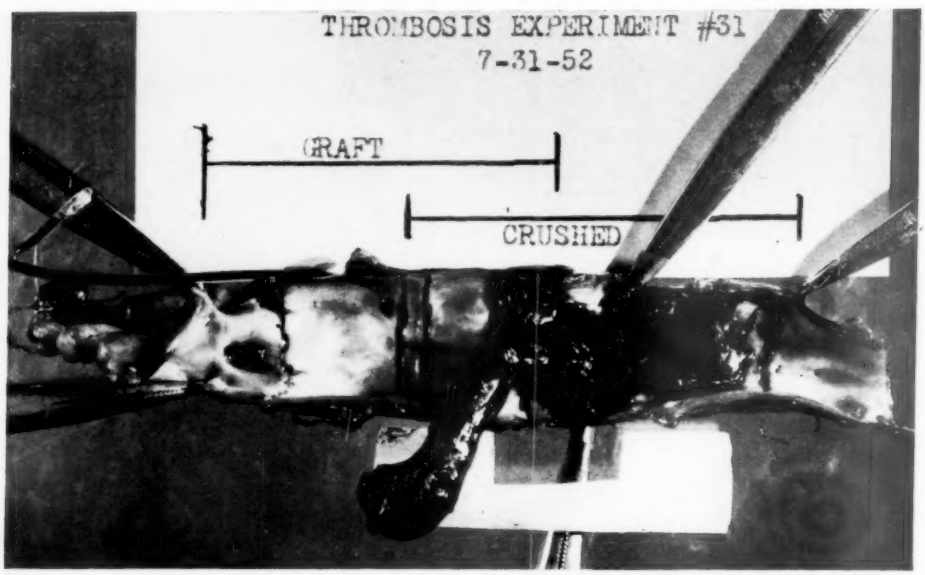


Fig. 4.—Illustration showing a freeze-dried graft which has been implanted into the recipient aorta. The aorta superior to the graft and the upper half of the graft have been crushed. The experimental animal was autopsied in twenty-four hours. The injured artery shown here was completely occluded by the thrombus which had extended down into the freeze-dried graft but was not attached to it at any point, other than at the superior suture line where the graft passively displayed the reversed P.D. of the injured artery above it. Freeze-dried grafts were very difficult to thrombose by any type of mechanical injury.

In the four fresh aortic grafts whose P. D. did not return to normal within twenty-four hours, and in two which later developed long-standing positive intimal potentials, complete occlusion occurred (Fig. 3).

Conversely, freeze-dried grafts, which are electrically inert tissues, having undergone cellular death in the process of lyophilization, displayed no P. D. on repeated determinations. The freeze-dried grafts were purposely crushed, transected, and subjected to long exposure to room temperatures after reconstitution in physiologic saline solution. In spite of this treatment they displayed no P. D. and did not thrombose after implantation and/or injury (Fig. 4). Their loss of P.D. apparently was an important factor in their resistance to

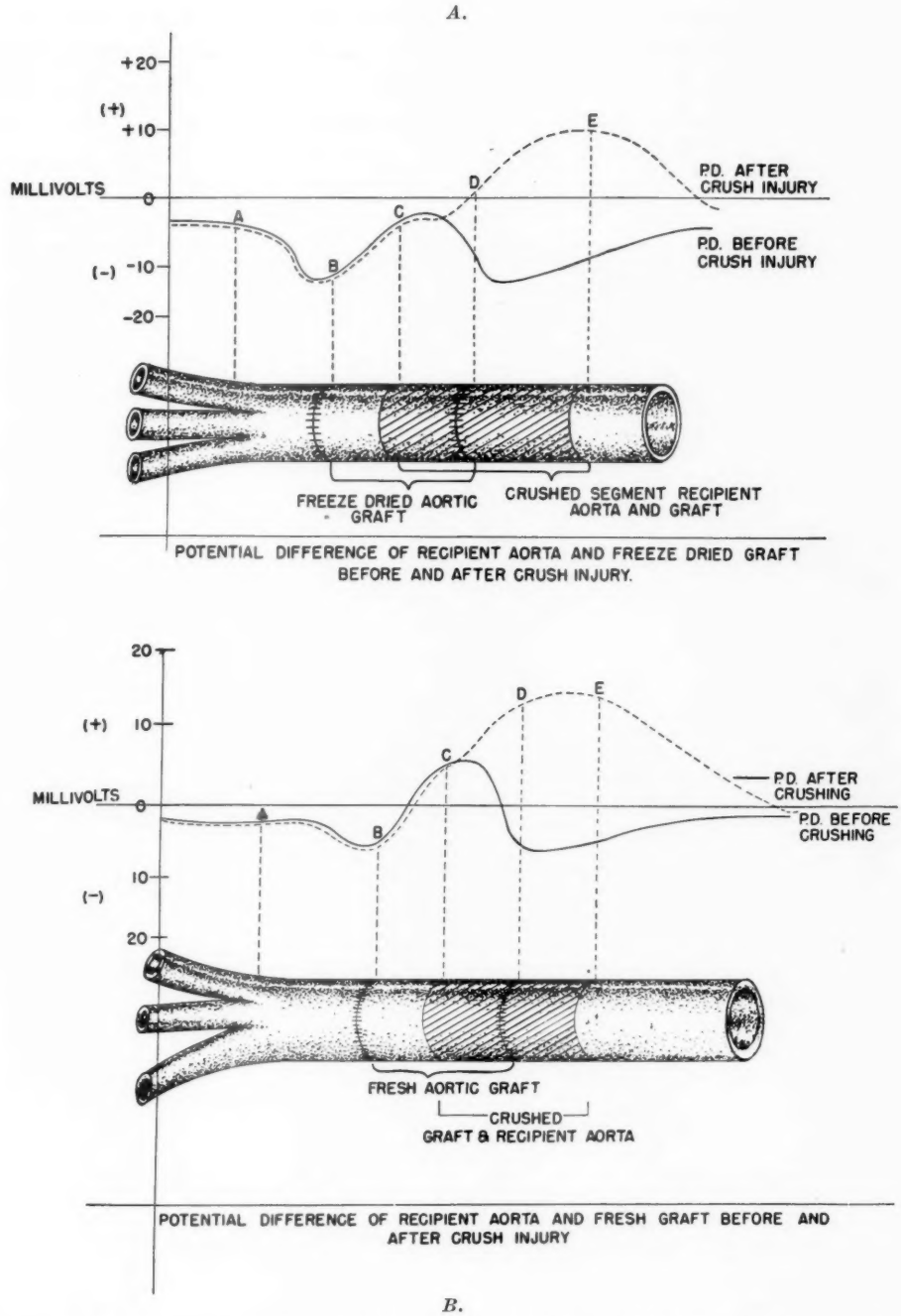


Fig. 5.—Schematic diagram of (*A*) the reversal of P.D. in the superior recipient artery and unchanged P.D. in the freeze-dried graft after crush injury compared to (*B*) the reversed P.D. of the fresh graft before injury increased by injury and the reversal of P.D. of the superior recipient aorta after crushing.

clotting (Fig. 5). There has been no correlation between the loss of intima and thrombosis. It has been shown histologically that, following freeze-drying, aortic segments lose their intima within a short time after implantation.

However, the intrinsic P. D. in the vessel is not the only bio-electric factor involved. It appears that the electromotive force in the dissected injured tissues surrounding the vessels may play an important part in the subsequent clotting of the vessel and/or its graft.[2]

Fig. 6.

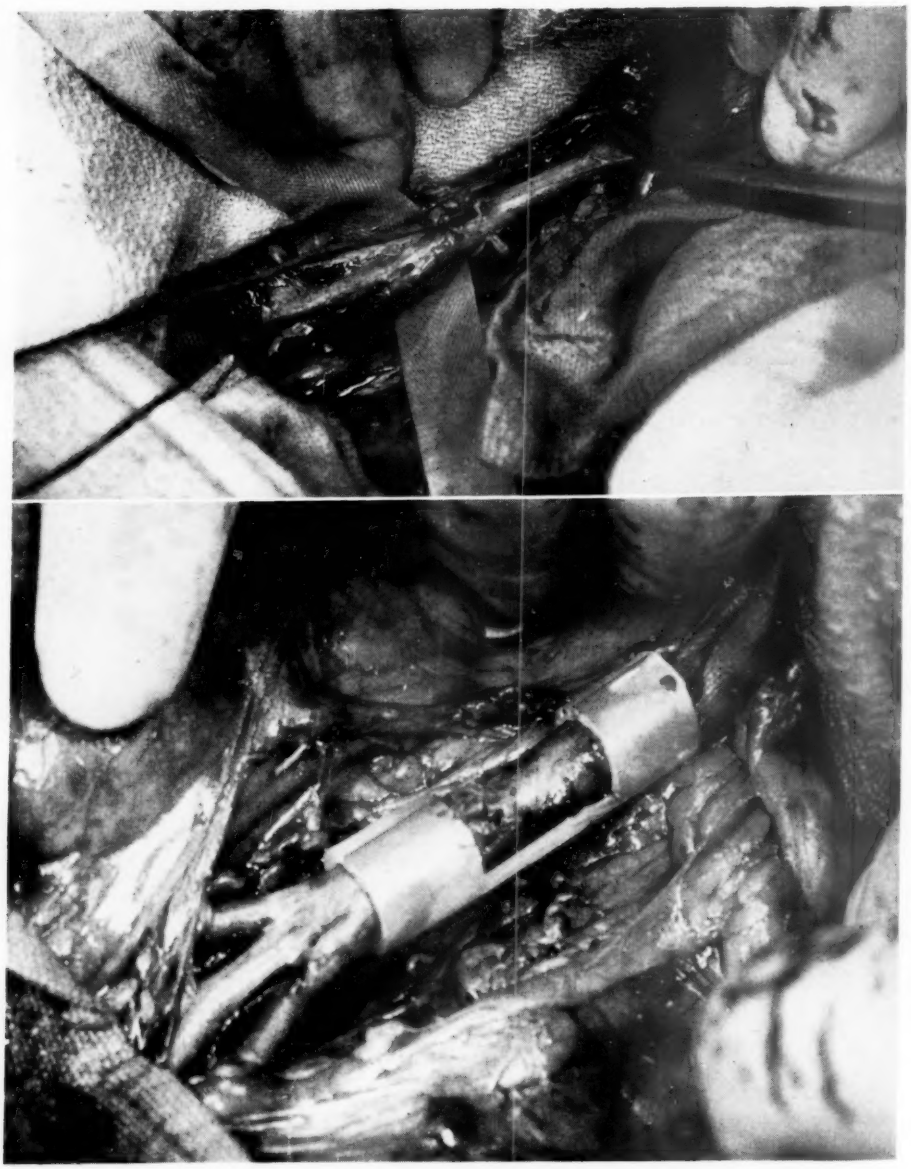


Fig. 7.

Fig. 6.—Illustration showing process of recording P.D. of an exposed abdominal aorta during crushing procedure.

Fig. 7.—Photograph of polyethylene insulator applied to damaged aorta after crush injury. Final P.D. measurements of injured abdominal aorta have been made.

A mathematical analysis of the series of daily long-term measurements across the walls of fresh and freeze-dried aortic grafts and the recipient arteries has shown that a great deal of electrical reaction takes place, not only between the grafts and the recipient aorta, but also between the vessels and their surrounding tissues.[2] Initially, the P. D. measured across the freeze-dried graft is the result of electromotive force in the recipient aorta and surrounding tissues. The freeze-dried graft has no intrinsic electromotive force and little resistance when first implanted. The P. D. of a freeze-dried graft and the recipient aorta have a relatively constant relationship with each other from day to day.

The P. D. of the fresh graft compared to that of the surrounding tissues and the recipient artery shows a large varying response between the graft, the aorta, and the surrounding tissues. The large P. D. variations occurring on the sixth and twelfth days may be correlated with the known periods of maximum antigenic response between the living homograft and the recipient tissue.[2]

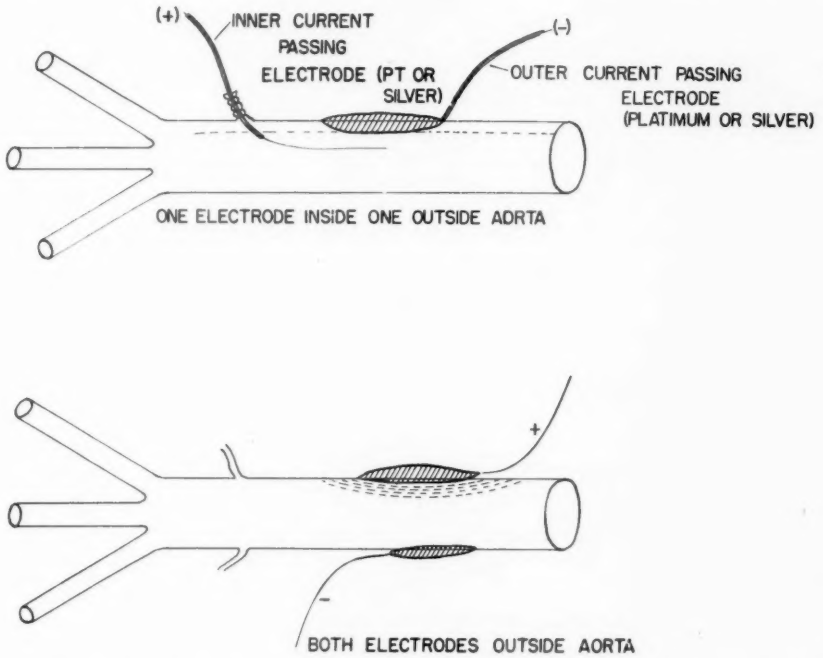


Fig. 8.—Schematic illustration of the two techniques used to apply a current across the normal blood vessel. *Top,* One electrode inserted through a branch into the lumen of the vessel, the other electrode applied to the adventitia. *Bottom,* Both electrodes applied externally to the adventitia of the blood vessel.

The electromotive force of the surrounding tissues has an effect on the measured P. D. of the graft. Positive potentials resulting from trauma to the surrounding tissues accentuate the injury potentials of the vessels themselves. This fact would serve to stress the need for extremely careful atraumatic dissection in the exposure of blood vessels.

If a long segment of blood vessel is severely crushed (Fig. 6), and if segments of the injured vessel are then carefully insulated with tightly applied sections of polyethylene tube (Fig. 7), sealed to the adventitia with mineral oil, gross mural thrombi will form only on the uninsulated areas during the first

twenty-four hours. The measured P. D. of the successfully insulated areas are invariably much lower than those of the uninsulated areas. This, we feel, is due to the loss of volume conduction from the surrounding tissues through the insulated areas. This is predicted from Kirchoff's Law:

$$\text{P. D. or } E_t = E_I + I_t R$$

where E_t is the total measured P. D.; E_I, the intrinsic electromotive force of the specific tissue; I_t, the current flowing through the whole circuit due to other sources of electromotive force; and R, the resistance of the whole circuit. $I_t R$ is that fraction of the measured P. D. caused by volume conduction. If $I_t R$ is large, then successfully insulating segments of vessel should reduce the measured P. D. through the insulated areas. This occurs as predicted. Control experiments were made with a metal pseudoinsulator identical in all respects to the polyethylene insulator except that it was a good electrical conductor. In no case did it prevent thrombosis. The thrombi formed in these experiments are histologically similar to spontaneous thrombi which have been studied.[4]

To determine if the currents produced by the P. D. can cause thrombosis in vivo, an artificial P. D. of the same polarity as the injury P. D. was applied across the blood vessel wall (Fig. 8). Thrombi invariably formed on the wall beneath the positive electrode. Carefully quantitated current flows of this type indicated that the current passed per unit area necessary to clot the vessel was of the same magnitude as that measured in injured areas.[3]

When a damaged aortic segment displays a positive intimal P. D. of + 5 mv. (an average injury P. D.), and has a resistance of 70 ohm centimeters square, then 0.7 μa of current per square millimeter will flow across the injured wall. These current flow measurements are predicted from:

$$I_w = \frac{e \text{ (mv.)}}{R \text{ (ohms)}}.$$

Then, $I = \frac{-5 \text{ mv.}}{70 \text{ ohm cm.}^2} = 72 \ \mu\text{a/cm.}^2 = 0.7 \ \mu\text{a/mm.}^2$ current flow through the injured vessel wall.

This amount of current passed across the normal aortic wall should cause thrombosis. Actually, the thrombosis of an entire 3 cm. segment of aorta has been caused by the passage of a current of 0.4 μa per square millimeter for a period of four hours.

Abramson[6-8] has shown that white blood cells and red blood cells are attracted to the positive pole of an electrophoretic cell. Recently, this has also been shown to be true for platelets.[9] If an electrode pair is placed in heparinized blood in vitro and a current is then passed between the two electrodes, the weight of blood elements precipitated on the positive electrode of the cell is directly proportional to the coulombs of current passed between the two electrodes.[3]

CONCLUSIONS

The theory is advanced that the injury currents caused by trauma to blood vessel walls and the surrounding tissues may create an electrophoretic force

which attracts and holds negatively charged platelets, red blood cells, white blood cells, and proteins against the injured wall. On this basis these bio-electric phenomena may constitute one of the etiological factors in thrombosis.

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DISCUSSION

DR. ROBERT B. BROWN (Bethesda, Md.).—Our clinical experience with freeze-dried arterial homografts has been very limited. We have used these grafts in human beings with the expectation that they will show a resistance to thrombosis comparable to that which has characterized their implantation in the experimental animal by Dr. Sawyer and Dr. Pate. A probable or, at least, possible explanation for this freedom from thrombosis has just been presented.

The period of follow-up has been short, but we have no reason to believe that the few human freeze-dried arterial homografts which we have implanted have not remained patent to date.

One patient, a young man aged 22 years, presented himself last summer with a very obvious complete thrombotic obstruction of the common iliac artery on the right. The vessel was explored and at operation it was found that the thrombus extended from 2 cm. below the aortic bifurcation down through the external iliac and femoral arteries to the level of the deep femoral. The thrombosed segment was excised and the defect was bridged with a freeze-dried graft, rather, I should say, with freeze-dried grafts. No single graft of the required length was available, so two grafts were sutured together, end to end.

Following this procedure the blood supply to the right lower extremity was excellent with easily demonstrable peripheral pulses. It remained so until recently when the patient returned with signs of recurring obstruction as evidenced by diminishing peripheral pulsations.

An arteriogram was made and it demonstrated partial obstruction at a level which we estimated was at or just below the lower anastomosis. When the obstruction progressed rapidly to completeness, re-exploration was performed. The patient's own vessel both proximal and distal to the graft was thrombosed, but the major portion of the graft and the graft-to-graft suture line were free from thrombosis.

The distal obstruction was excised and the defect repaired by regrafting. The proximal obstruction was partially relieved by removing the thrombotic material, but subsequent flow was poor and we do not feel that a permanent increase in blood supply has been effected. Probably nothing short of grafting a new aortic bifurcation will accomplish the latter.

DR. JOHN T. REYNOLDS (Chicago, Ill).—I would like to comment on Dr. Brown's discussion. This summer, I happened to be in Strasbourg at the European Vascular Society

meeting where Professor René Fontaine, whom some of you may know, presented two patients on whom he had made arteriograms after arterial substitution. In one a common iliac artery had been replaced two years previously, and in the second a femoral artery had been replaced some six or eight weeks before. In both of these cases the functional result was excellent. In both of these cases arteriograms made to demonstrate the patency of the vessel were followed within one hour by thrombosis and loss of the vessel and of the limb. I call your attention to this because I feel that we should have very strict indications for making arteriograms after substitution. While this is true when the functional result is obviously good, the contraindication in patients who have questionable functional results seems even stronger when the threat of possible complete loss of circulation is present.

DR. SAWYER (closing).—There is increasing evidence in the literature, and I think we have some evidence too, that heparin may prevent intravascular thrombosis because it is a highly negatively charged ion, which attaches itself to the proteins flowing in the blood stream. A group of investigators at Cornell under White, Hirsch, and Texter have been measuring the increase in negative flow potentials of various blood proteins. The changes in potential difference are caused when heparin is added to the elements which actually participate in thrombus formation. The flow potentials are then measured. The group has been definitely able to demonstrate that the negative zeta potentials of the various protein elements, including fibrinogen and prothrombin, are markedly increased when heparin is added to the molecules flowing through the flow chambers.

STUDIES ON LYSIS OF EXPERIMENTAL PULMONARY EMBOLI USING TRYPSIN

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(From the Department of Surgery, Duke University School of Medicine)

THE effectiveness of the anticoagulant drugs in the prevention and therapy of thromboembolic disease is well established. An increasing amount of attention is now being given to the series of events which leads to recanalization of the vessel after the hemostatic process has occurred. Fibrinolytic enzymes, by their ability to digest the fibrin clot, should play a significant role in this phase of study. Recently, purified preparations of pancreatic trypsin have become available. These appear less toxic than earlier preparations and, indeed, have been administered intravenously to animals and man without outstanding toxic reactions.[1] These preparations of trypsin possess strong proteolytic and fibrinolytic powers and, if shown to be sufficiently devoid of toxicity, should theoretically prove to be useful agents in treatment of the various pathologic processes manifested by occlusion of arterial or venous channels due to intravascular clotting.

The present study represents an effort to evaluate the effectiveness of one of these preparations of trypsin (Enzar†) in the lysis of experimental pulmonary emboli in dogs, to observe changes in certain components of the blood which are involved in the clotting mechanism, and to observe any gross or microscopic evidence of tissue damage produced in certain vital organs of the animal by this drug.

MATERIALS AND METHODS

Mongrel dogs weighing from ten to twelve kilograms were used in this experiment. Clots of uniform size (5 cm. in length and 8 mm. in diameter with an average volume of 1.3 c.c.) were prepared by using the animal's own blood. In one group of eleven animals, the blood was mixed with 40 mg. of barium sulfate per cubic centimeter just prior to clotting, in order to render the clot radiopaque. The clot was then allowed to retract for one hour, after which the volume was recorded and, with the animal under Nembutal anesthesia (35 mg. per kilogram), the clot was introduced by way of the jugular vein into the pulmonary circulation and an x-ray picture was obtained to visualize the position of the clot (Fig. 1). Seven animals of this group were then given intravenous trypsin (15,000 and 20,000 U. per kilogram) at eight-hour intervals over a twenty-four or forty-eight hour period. The remaining four dogs were used for controls and received 5 per cent dextrose in water instead of trypsin.

This study was supported in part by a Duke University Research Council Grant.

Read at the meeting of the Society of University Surgeons, St. Louis, Mo., Feb. 12-14, 1953.

*Public Health Service Research Fellow of the National Heart Institute.

†Enzar was generously supplied by Dr. Marvin Ziporyn of Armour Laboratories.

The same experiment was then repeated in seven animals without addition of barium sulfate to the clot, in order to remove any influence of foreign material on lysis.

Samples of blood were drawn at periodic intervals from all animals and an estimation of serum fibrinolysis was made by a modification of the method of Lewis and Ferguson.[2] Serum antifibrinolytic activity was determined by the method of Clark, Cliffton, and Newton.[3] An estimation of fibrinogen content was made by determination of the fibrinogen index as described by Borgstrom.[4] This procedure is based on the clotting time of plasma in which all essential

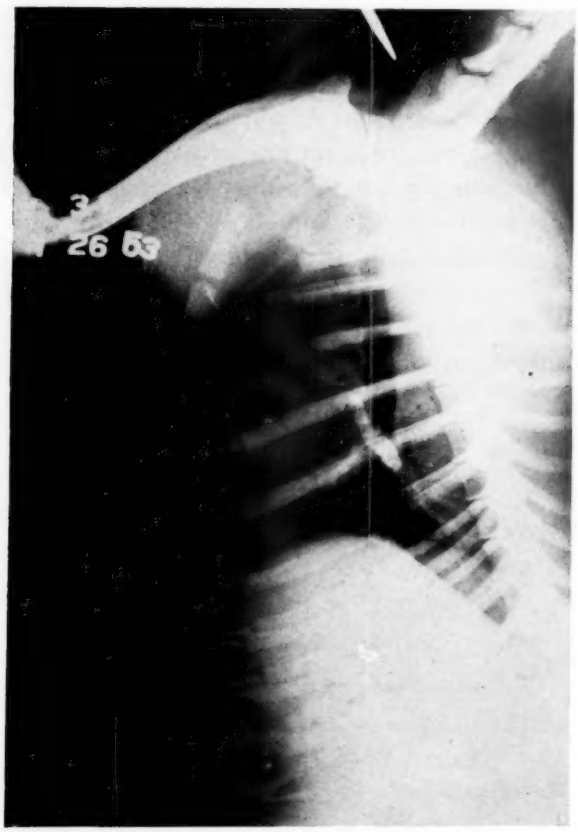

Fig. 1.—Roentgenogram showing position of the radiopaque clot in a main pulmonary artery.

components are supplied except fibrinogen. This clotting time is then compared to that of a normal control. The Quick one-stage "prothrombin" time and Lee-White clotting time were also determined. At the end of the experimental period all animals were sacrificed, the clot was removed, the volume recorded, and necropsy performed. The introduction of an intact clot was unsuccessful in four animals due to disparity in size of the clot and the jugular vein.

RESULTS

Preliminary experiments in anesthetized dogs indicated that doses of 15,000 to 25,000 U. per kilogram (body weight) of trypsin, given at a rate not to

exceed 3000 U. per minute, could be given without reduction in blood pressure or other observable physiologic change. These doses were sufficient to induce definite fibrinolysis for from six to ten hours in the serum of the animals, suggesting an eight-hour dosage schedule in order to maintain this effect during a treatment period.

Serum fibrinolytic activity was found in all animals for eight to ten hours following each trypsin injection, whereas no fibrinolytic activity was present in blood obtained from control animals. Fig. 2 shows the serum fibrinolytic activity in one animal after a single injection of trypsin (20,000 U. per kilogram). Concomitant with the rise in serum fibrinolytic activity there occurred a fall in antifibrinolytic titer which lasted from twelve to twenty-four hours.

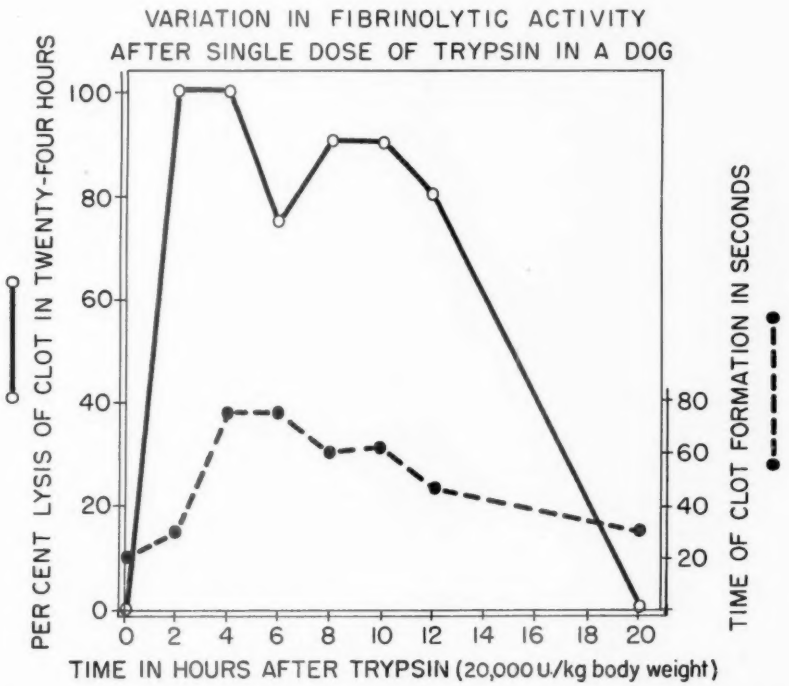

Fig. 2.—Graph showing percentage of lysis of standard clot in twenty-four hours and delay in formation of standard clots by fibrinolytic sera.

Fig. 3 shows the effect of a single injection of trypsin (20,000 U. per kilogram) on antifibrinolysis in a dog. The Quick one-stage prothrombin time was elevated from four to eight hours following each trypsin injection in all animals. Fig. 4 shows the alteration in percentage of normal prothrombin concentration in a dog after an injection of trypsin. It should be pointed out that the one-stage Quick prothrombin determination is not a true measure of prothrombin content in the presence of deficiencies of fibrinogen or prothrombin activators. The prothrombin consumption test of Warner, Brinkhous, and Smith,[5] a more accurate measurement of prothrombin content, also showed a reduction in prothrombin content following trypsin. There was evidence of a marked reduction of serum fibrinogen in all animals receiving trypsin, as revealed by

determination of the fibrinogen index.[4] The Lee-White clotting time was prolonged beyond thirty minutes in seven of eight dogs at some time while they were under the influence of trypsin; however, the prolongation of clotting time could

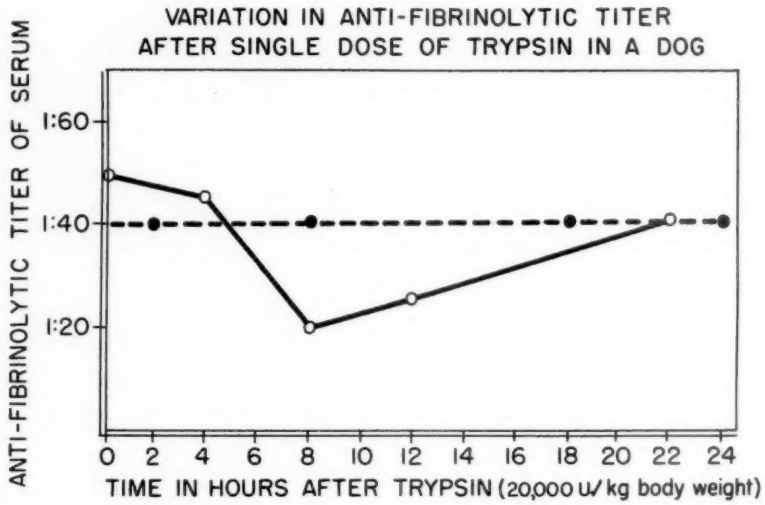
VARIATION IN ANTI-FIBRINOLYTIC TITER
AFTER SINGLE DOSE OF TRYPSIN IN A DOG
ANTI-FIBRINOLYTIC TITER OF SERUM
1:60
1:40
1:20
0 2 4 6 8 10 12 14 16 18 20 22 24
TIME IN HOURS AFTER TRYPSIN (20,000 u./kg body weight)

Fig. 3.—Graph showing fall in serum antifibrinolytic titer (*heavy line*) as compared with the titer in a control animal (*broken line*).

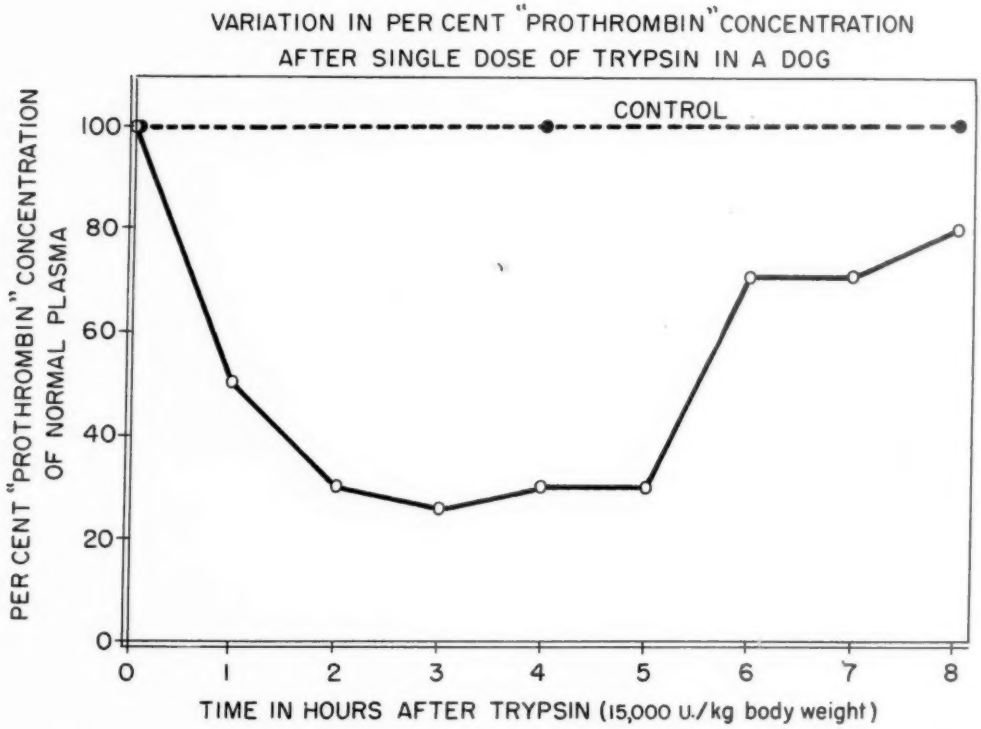

Fig. 4.—Graph showing the alteration in percentage of normal prothrombin concentration in a dog after an injection of trypsin.

not be correlated with the amount of individual or total dosage of trypsin. In general, larger doses produced definite prolongation of the clotting time.

The results relative to the reduction in volume of the barium clot in the trypsin-treated and control animals are shown in Table I. The control animals showed 20 to 30 per cent reduction in clot volume in twenty-four to forty-eight hours, whereas the clot was reduced 55 to 100 per cent in the dogs receiving trypsin. More striking is the fate of the pure clots (no barium present) in trypsin-treated animals shown in Table II. In this group, there was practically complete lysis of all clots in twenty-four hours, whereas clots in the control animals showed only 20 to 30 per cent reduction in size.

TABLE I. PERCENTAGE OF VOLUME REDUCTION OF PULMONARY CLOTS* IN DOGS

DOG	DOSAGE OF TRYPSIN (U. PER KG. EVERY 8 HOURS)	LENGTH OF EXPERIMENT (HOURS)	CONTROL (PER CENT)	TREATED (PER CENT)	INFARCTION
16	--	48	15		Yes
21	--	48	30		Yes
22	--	48	33		Yes
30	--	24	33		No
18	15,000	48		86	No
24	15,000	48		55	No
25	20,000	48		91	No
26	20,000	48		100	No
28	20,000	48		80	Yes
27	20,000	24		75	No
32	20,000	24		56	Yes

*Mixed with barium sulfate (40 mg. per cubic centimeter).

TABLE II. PERCENTAGE OF VOLUME REDUCTION OF PULMONARY CLOTS* IN DOGS

DOG	DOSAGE OF TRYPSIN (U. PER KG. EVERY 8 HOURS)	LENGTH OF EXPERIMENT (HOURS)	CONTROL (PER CENT)	TREATED (PER CENT)	INFARCTION
36	--	24	38		Yes
40	--	24	30		No
42	--	24	0		Yes
33	15,000	24		100	No
34	15,000	24		100	No
38	20,000	24		100	No
39	15,000	24		100	No

*No barium sulfate added.

In a total of twelve dogs receiving intravenous trypsin in total amounts ranging between 450,000 and 1,200,000 U., death occurred in only one animal. This death presumably occurred from the effect of the experimental pulmonary embolus and was not attributable to the injection of trypsin, since the animal had received only a small amount of the drug. One of eight control dogs died and at autopsy was found to have an extensive infarct* of one lung, secondary to embolism. All remaining animals survived the embolus, and at autopsy five of the seven remaining control animals showed gross evidence of segmental

*The term "infarct," as used here, denotes an area of gross hemorrhagic consolidation which did not show necrosis on microscopic study.

infarction of the lung supplied by the blocked pulmonary artery, whereas in only two of eleven treated animals was there gross evidence of infarction present when the dogs were sacrificed. Additional gross findings at autopsy consisted of the presence of small focal hemorrhages in the wall of the gall bladder in five animals and petechial hemorrhages in the pancreas and spleen in two animals. All of these animals received the larger dose of drug (20,000 U. per kilogram).

No significant microscopic changes were noted in the animals receiving 15,000 U. per kilogram. Of the five animals showing changes in the gall bladder, the mucosa was normal in four, the hemorrhages being subserosal without associated inflammatory reaction. One animal showed a definite acute cholecystitis. Microscopic changes in that portion of the lung associated with the pulmonary embolus consisted of varying degrees of hemorrhage and atelectasis without tissue necrosis. These findings are to be reported in more detail in a separate communication.

DISCUSSION

The phenomenon of fibrinolysis, whereby a preformed clot is digested in its serum, occurs in certain pathologic processes as, for example, in certain types of shock, severe infections, blood dyscrasias, or toxemias of pregnancy.[6] In normal circulating blood, fibrinolysin* is present as an inert proenzyme which, on occasion, may become activated by kinases which are found in many tissues.[6] An antifibrinolysin† also exists in blood.[7] The degree of activation of profibrinolysin depends on a delicate equilibrium between activators and inhibitors in the blood. When the naturally occurring profibrinolysin becomes activated, as in the afore-mentioned disease processes, a bleeding tendency develops which is probably due to enzymatic digestion not only of the fibrin clot but also of fibrinogen and other proteins involved in the process of blood coagulation.[6]

The effect of trypsin on this fibrinolysin-antifibrinolysin equilibrium of blood is not understood. There is evidence which suggests that it may activate naturally occurring profibrinolysin.[8] Some reports in the literature suggest that trypsin increases the coagulation of blood,[9] others, that it acts as an anticoagulant.[10] This difference in behavior probably is dependent on the dose administered. Using a sensitized clotting test[11] to detect hypercoagulability of the blood, it was found that, following injection of small amounts of trypsin, hypercoagulability of the blood did occur, but following larger amounts the blood became hypocoagulable. Thus, small amounts of the drug produce hypercoagulability, presumably by conversion of prothrombin to thrombin,[9] whereas larger doses produce an anticoagulant effect by reduction of prothrombin and fibrinogen.[1] The alteration in the clotting mechanism found in these experiments after large doses of trypsin were administered intravenously appears transitory in nature.

*Synonyms: plasmin, tryptase, lysin.
†Synonyms: antiplasmin, antitryptase.

The fall in serum antifibrinolysin following trypsin injection can be explained on the basis of the irreversible chemical reaction[12] occurring between this substance and trypsin.

Serum albumin is not digested by trypsin unless it is denatured,[13] but the action of trypsin on other serum proteins has not yet been reported. In the present study, in five dogs in which measurement of total serum proteins and nonprotein nitrogen were made before and after large doses of trypsin, only minimal changes occurred.

Innerfield, Angrist, and Benjamin[1] have reported that large single intravenous injections of a trypsin preparation (Tryptar*) have produced disappearance of thrombi formed by the injection of sodium morrhuate into the ear vein of the rabbit and the femoral vein of the dog. In the present study, dogs treated with trypsin showed a greater degree of lysis of pulmonary emboli than occurred in untreated animals. The influence of clot retraction on reduction in size of the clot must be considered. There was no evidence of propagation of any clots in either the treated or untreated animals. When using clots not containing barium sulfate, it was not possible to be absolutely certain that the clot was intact and had not been disrupted during injection.

Previous reports concerning trypsin toxicity have dealt with the shock state associated with use of this drug. Innerfield has found that the occurrence of shock is related to the speed of injection of the material, and the present study confirms this finding. However, when large doses of trypsin were used, widespread focal hemorrhages occurred in some animals. The lower dosage (15,000 U. per kilogram) produced a fibrinolytic effect without the hemorrhagic manifestations, and even smaller doses of the drug may prove more desirable.

Recently, trypsin has been shown to produce certain changes in red cells in vitro, consisting of a slight increase in fragility[14] and certain changes in antigenic properties.[15] The significance of these findings awaits further elucidation. Also, the effects of trypsin on erythrocyte survival rate, hemolysis, and the other cellular elements of the blood must be determined. There are many other aspects concerning the fate and excretion of trypsin, and its effect on body tissues and organ function, which require further study.

SUMMARY AND CONCLUSIONS

Experimental pulmonary emboli, using clots of uniform size, have been produced in dogs. One group of animals has been treated with large doses of intravenous trypsin, and the incidence of pulmonary infarction and reduction in clot size have been compared with the same factors in a group of control animals. Studies on the blood of the animals receiving trypsin revealed a high titer of serum fibrinolytic and a low titer of serum antifibrinolytic activity, with a decrease of blood prothrombin and fibrinogen and a prolongation of the Lee-White clotting time. These alterations in the blood appear to be transitory in nature. Five of seven control dogs developed gross pulmonary infarction, whereas only two of eleven dogs receiving trypsin developed infarcts. There

*Armour Laboratories.

was evidence of partial to complete clot lysis, as judged by decrease in clot size, in all animals receiving trypsin, with a much smaller reduction of clot size in control animals. Further evaluation of this drug for possible use in man to alter the hemostatic mechanisms appears warranted.

Acknowledgment.—We wish to express our thanks to Dr. R. J. Reeves and his associates in the Department of Radiology and Dr. Walter Benson of the Department of Pathology for their assistance in this study. We are also indebted to Mrs. Norma W. Mann, Elbert L. Fisher, and Hugh M. Shingleton for their technical assistance.

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DISCUSSION

DR. J. GARROT ALLEN (Chicago, Ill.).—Four years ago before this Society, we presented the concept of a dynamic blood coagulation, that is, that the clotting process is in continuous function to prevent abnormal bleeding. This excellent paper by Dr. Shingleton and his colleagues presents data that add further support to the dynamic concept. It is well known to surgeons that, once a hematoma develops in a wound, it is seldom necessary to evacuate the clot because in about seven to ten days this clot will liquefy. When the clot has liquefied, the blood can then be aspirated if necessary. Trypsin, of course, greatly accelerates this process. As Dr. Shingleton pointed out, if the digestive action of trypsin is too great, hemorrhage results because no fibrinogen remains.

There is another agent which I think, personally, holds an even greater future in the problem of clot lysis. This is the normally occurring fibrinolytic enzyme present in human plasma. This fibrinolytic enzyme normally resides in an inactive state, during which it is known as profibrinolysin. This proenzyme can be easily extracted from plasma and, when activated by Streptokinase, it has a powerful fibrinolytic action. Activated human fibrinolysin, when injected into dogs, rapidly destroys all circulating fibrinogen. It produces almost no systemic reactions although, if all fibrinogen is removed, hemorrhage of course will occur.

Human fibrinolysin should be available in large quantities as a by-product in the blood fractionation program. Possibly, by activating this material with Streptokinase, it can be employed in the digestion of intravascular clots.

DR. DAVID V. HABIF (New York, N. Y.).—Many investigators are currently evaluating trypsin given intravenously and they have found that, regardless of the dose or dilution employed, a certain number of patients have a chemical phlebitis at the infusion site. I have had the privilege of working with one of our third-year medical students, George Kleinfeld, who noted that the pH of trypsin in normal saline solution was 4.2, which is comparable to the pH of dilute vinegar. As the result of the addition of Sorensen's buffer, the pH may be brought to 7.4, and this, he has noted, leads to a marked decrease in the number of phlebitic reactions. If a daily infusion is given beyond five days, local phlebitis is markedly diminished but not eliminated. No loss of tryptic activity is apparent clinically as the result of buffering prior to injection.

DR. SHINGLETON (Closing).—I would like to thank the discussers for their comments. In regard to Dr. Allen's comments, we did not make a study of the platelets in these experiments. Also, I agree with Dr. Allen that probably the most promising substance will prove to be the natural serum proteolytic enzyme which can be activated and injected.

THE EFFECTS OF ADRENAL MEDULLECTOMY AND SYMPATHECTOMY ON THE CIRCULATORY DYNAMICS OF NORMAL DOGS

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AT THE moment, the essence of the problem of essential hypertension seems to lie in the mechanisms which control the tone and caliber of the smaller blood vessels. For, according to the laws of hemodynamics, the pressure in the aorta and larger arteries is controlled by the cardiac output, the viscosity of the blood, and the frictional resistance which is imposed primarily by the small arteries, arterioles, and capillaries. In the control of arteriolar tone, humoral and neurogenic factors have been most strongly implicated. Surgeons in the past have been directing their efforts at the sympathetic nervous system in an attempt to modify arteriolar tone, but recently more emphasis has been ascribed to the adrenal factors in the maintenance of vascular tone and reactivity. The clinical status of sympathectomy in the treatment of essential hypertension has been most widely studied by Smithwick,[1] and the initial results of bilateral extensive-to-complete adrenalectomy on man have been reported by Thorn[2] and Zintel.[3] Despite the vast amount of work and speculation at both the experimental and clinical levels, the exact relationship of both the sympathetic nervous system and the adrenal glands to hypertension remains unclear.

It has been shown by Cannon[4] and by Bacq, Brouha, and Heymans[5] that in both the cat and dog at rest the arterial pressure returns to normal after a complete removal of the sympathetic chains. The sympathectomized dog, in fact, could run and fight as successfully as other dogs, and this would be inconceivable unless both general and local redistribution of vascular flow and resistances were possible by other mechanisms or substances. Even in man, total sympathectomy has been accomplished by Grimson[6] without undue loss of vascular reactivity, and the physiologic effects of lumbodorsal sympathectomy in man have been surprisingly few, as carefully studied by Simeone.[7] In man and in animals, therefore, removal of the sympathetic nerves enlarges the vascular bed only temporarily, and after a variable period of time the arterioles return to normal caliber through the action of an intrinsic mechanism which is non-neurogenic, and presumably humoral, in character.

The relationship of the adrenal gland to hypertension has been widely studied since the initial observation by Goldblatt[8] that total adrenalectomy interfered with the production and maintenance of experimental hypertension produced by renal ischemia. The majority of work has concerned the interrelationships between the adrenal cortex and hypertension. Experimentally, Selye[9] has produced hypertension and its associated vascular lesions in animals

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by large doses of mineralo-corticoids or certain corticotrophic pituitary extracts, and Braun-Menendez[10] has emphasized the importance of sodium salts and the expanded extracellular fluid compartment in hypertension from desoxycorticosterone. Clinically, the association of hypotension and salt loss with Addison's disease (adrenal hypofunction) and the occurrence of hypertension and salt retention with Cushing's disease (adrenal hyperfunction) needs no further substantiation. Perera[11] reviewed the clinical and experimental data available and concluded: "No data have been presented thus far which establish the adrenal cortex as playing a primary causative role in hypertensive disease in man . . . we remain completely in the dark as far as possible mechanisms are concerned." Merrill[12] reached essentially the same conclusion but speculated further that "the quantitative interrelation of the adrenal steroids may be more important than the activity of the gland as a whole."

Heinbecker[13] summed up a bulk of experimental evidence, much of it his own, elucidating the interrelationships of the paraventricular nuclei, the neural hypophysis, the pituitary gland, and the adrenal to the pathogenesis of diastolic hypertension. The sympathetic nervous system and the adrenal medulla were regarded as homeostatic mechanisms for the rapid adjustment of peripheral resistance. Rather[14] emphasized the hyperplasia and hypertrophy of the adrenal medulla and the rise in the adrenal medulla to cortical ratio in clinical and experimental hypertension. The importance of adrenal medullary secretion and the sympathetic nervous system in the control of the release of ACTH has been clarified by Long and associates,[15, 16] and the role of epinephrine and ACTH in the activation of adrenal cortical secretions has been demonstrated by Vogt.[17] Clinically, also, the existence of both paroxysmal and sustained hypertension in patients with pheochromocytomas has been repeatedly observed.

The relationship of the sympathetic nervous system and epinephrine secretion to the production of ACTH, the influence of ACTH on the activation of the adrenal cortex, and the interrelationships of the cortical and medullary secretions to hypertension experimentally and clinically suggested the present investigations. The purpose of the investigations is to determine the effects of bilateral adrenal medullectomy and bilateral thoracolumbar sympathectomy on blood pressure, cardiac output, and peripheral vascular resistance.

METHODS

Dogs were used as the experimental animal. Studies were carried out first in animals in the control state, then after bilateral adrenal medullectomy, and finally after bilateral adrenal medullectomy followed by a complete thoracic sympathectomy.

Control Studies and Calculations.—The dog was anesthetized with veterinary Nembutal intravenously in a dose of approximately 30 mg. per kilogram. An intratracheal catheter was inserted and connected through inspiratory and expiratory valves so that the animal inspired room air; the expired air was collected in a Tissot spirometer. The volume of expired air was measured and corrected to standard temperature and pressure deviation conditions. The

fractions of oxygen and carbon dioxide in the expired gas were analyzed, using a Pauling oxygen analyzer for the oxygen tension in the expired gas and the Haldane apparatus for the carbon dioxide. These studies permitted a calculation of the oxygen consumption, carbon dioxide production, and respiratory quotient by the standard respiratory equations:

$$1.\ \dot{V}_{O_2} = \frac{\dot{V}_E}{1-F_{I_{O_2}}} \cdot F_{I_{O_2}} - F_{I_{O_2}} \cdot F_{E_{CO_2}} - F_{E_{O_2}}$$

$$2.\ \dot{V}_{CO_2} = \dot{V}_E \cdot F_{E_{CO_2}}$$

$$3.\ R = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$$

An intracardiac catheter was inserted into the right heart through the external jugular vein and its position in the right ventricle was verified by fluoroscopy and pressure tracings. A Cournand needle was placed in the femoral artery. Pressures from the right ventricle and the femoral artery were recorded through a Stratham strain gauge into the Brush oscillograph. The sample of blood drawn from the right ventricle was used as the mixed venous sample and blood from the femoral artery represented the arterial sample. The oxygen contents of the sample were analyzed in duplicate on the Van Slyke apparatus. Air samples were collected over a five-minute period, and blood samples were taken during the middle of the air collection by drawing blood slowly over a three-minute period. The cardiac output could then be calculated by the Fick principle:

$$\dot{Q}b = \frac{\dot{V}_{O_2}}{Ca_{O_2} - C\bar{v}_{O_2}}$$

The peripheral resistances in the systemic and pulmonary circuits were calculated in arbitrary units from the relationship

$$R_{systemic} = \frac{\text{mean systemic pressure}}{Qb}$$

$$R_{pulmonary} = \frac{\text{mean pulmonary pressure}}{Qb}$$

Operative Procedures.—Once the studies of pressure, flow, resistances, and oxygen consumption were established in the control state the animal was subjected to a bilateral adrenal medullectomy. The adrenals were exposed separately in staged operations approximately two weeks apart. The easiest ap-

proach was through a transthoracic transdiaphragmatic incision, dividing the musculature in the line of the tenth or eleventh intercostal space (Fig. 1, *A*). The middle adrenal vein was divided laterally, and the adrenal was rotated free except for the medial vascular attachments. A Pott's clamp was placed across the vascular pedicle of the mobilized gland, the gland was incised throughout

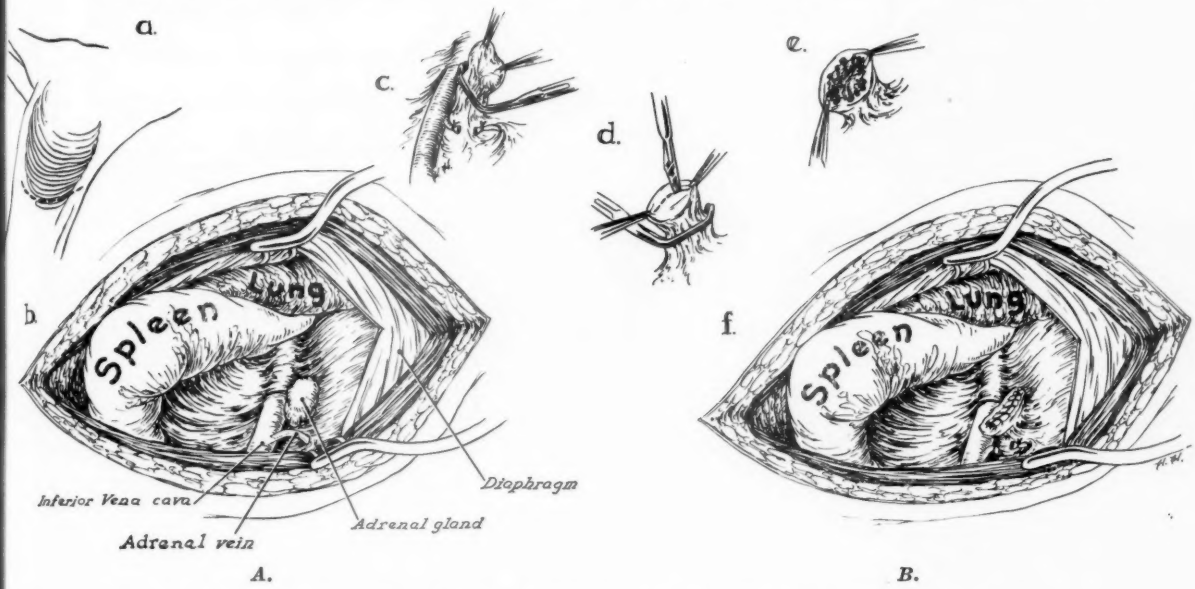

Fig. 1, *A* and *B*.—Diagram illustrating technique of adrenal medullectomy (see text).

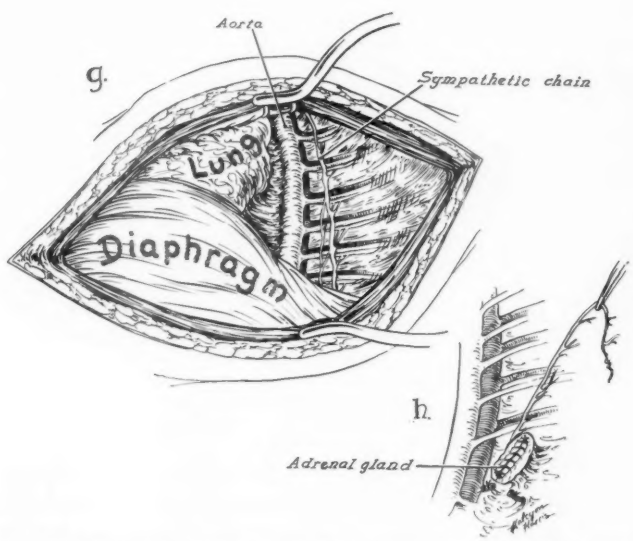

Fig. 2.—Diagram illustrating technique of sympathectomy.

its length, and the medulla was removed with a knife and curette (Fig. 1, *B*). The adrenal cortex was then sutured with a continuous mattress suture of arterial silk, and the wound was closed. Approximately two months was allowed to elapse, and then the previous studies and calculations were repeated.

The final procedure on the animals consisted in removing the entire thoracic sympathetic chain from the second or third thoracic ganglion down to and including the first and second lumbar portions of the sympathetic chain (Fig. 2). This was accomplished through a transthoracic incision going through the seventh or eighth intercostal space. Each side was operated upon separately. Approximately two months later the control studies were again repeated.

Each animal, therefore, served as its own control for each procedure. The animals remained in good health during the year of study and required no supportive therapy of any type.

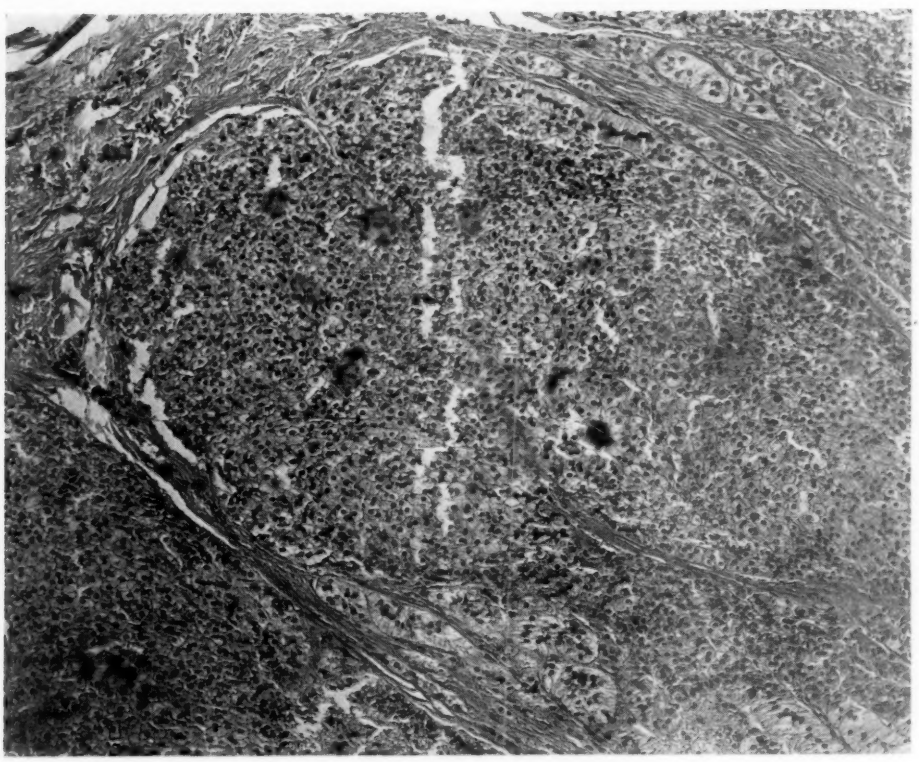

Fig. 3.—Photomicrograph showing histologic appearance of adrenal after medullectomy.

RESULTS

Completeness of Adrenal Medullectomy.—The first two animals in the series had bilateral simultaneous adrenal medullectomy and both of these animals died within forty-eight hours. The adrenal medulla was then removed from only one side at a time, the operations being staged ten to fourteen days apart, and the animals lived without any supplemental therapy. These animals were sacrificed after six weeks, and histologic studies of the remaining adrenals showed no disturbances in the cortex and no residual adrenal medullary tissue (Fig. 3). Similarly, one of the five animals on which studies were completed expired during cardiac catheterization after all operations had been completed, and sections of the adrenal on this animal showed no remaining medullary tis-

sue and no histologic changes in the cortex. It seems reasonable to assume, therefore, that the animals studied completely, five in number, had complete bilateral adrenal medullectomy.

General Status of the Animals.—All five animals on which operations and studies were completed remained in excellent health during the course of the experiments and afterward. They seemed normal in every respect and required no supplemental therapy of any type.

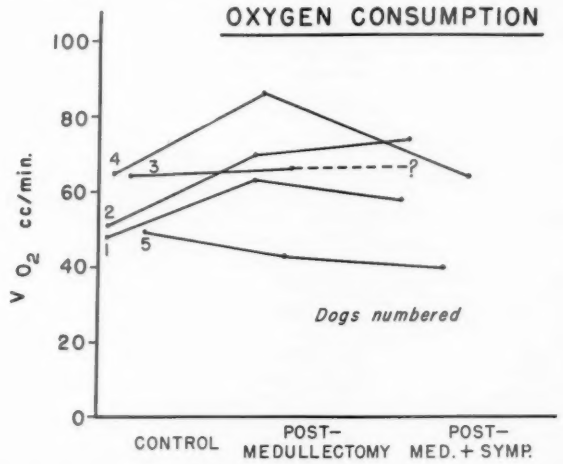

Fig. 4.—Graph showing effects of the procedure on oxygen consumption.

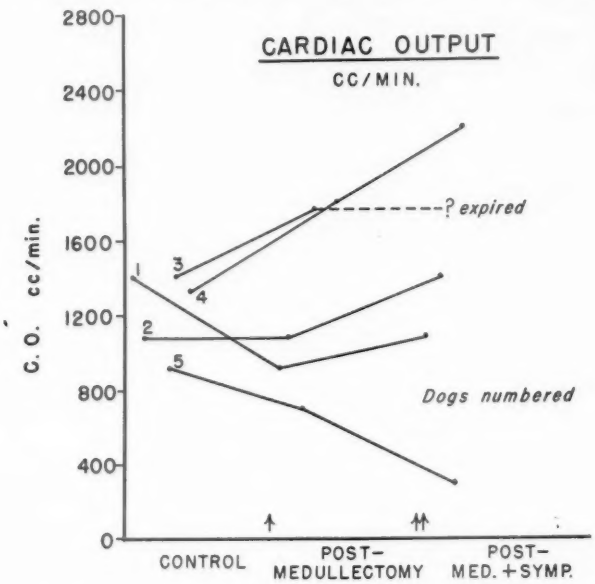

Fig. 5.—Graph showing effects of the procedure on cardiac output.

Effect on Oxygen Consumption.—The oxygen consumption averaged approximately 5 to 7 c.c. per kilogram per minute in the control state in all five animals and remained essentially the same after bilateral adrenal medullectomy. Complete thoracic sympathectomy did not alter the oxygen consumption significantly or constantly in the animals (Fig. 4).

Effect on Cardiac Output.—Assuming a 10 to 15 per cent error in the Fick method for measuring cardiac output as reasonably accurate, two of the five dogs showed a significant drop in cardiac output, two dogs showed a significant rise, and the other dog remained unchanged. The animals that showed a rise

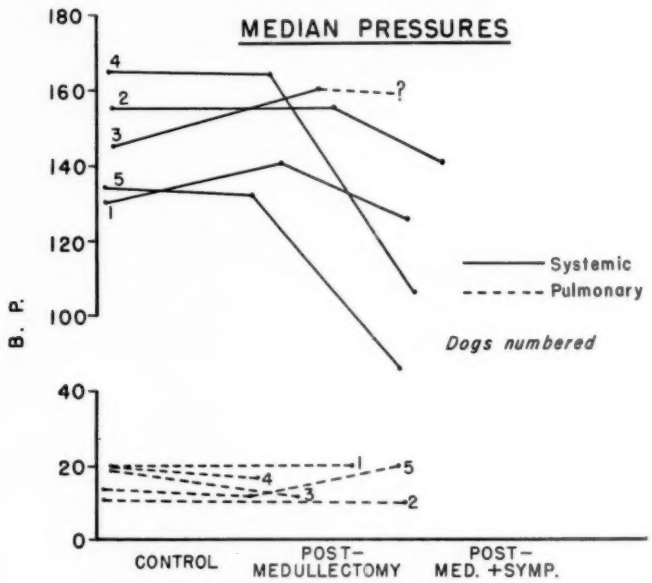

Fig. 6.—Graph showing effects of the procedure on blood pressure.

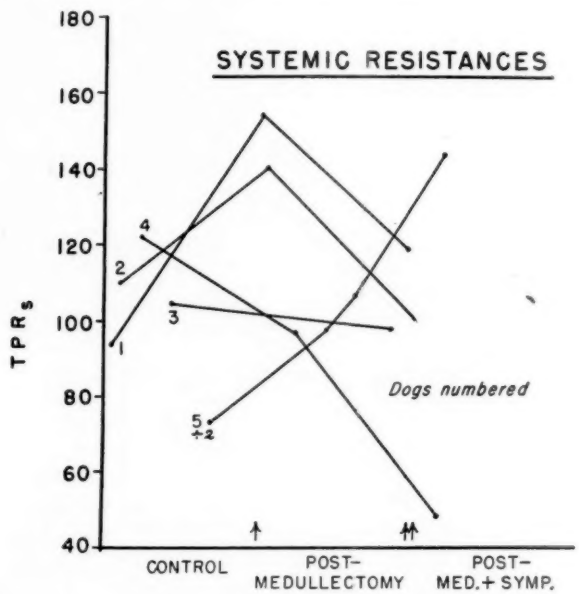

Fig. 7.—Graph showing effects of the procedure on systemic peripheral resistance.

after adrenal medullectomy showed an additional increase in cardiac output after sympathectomy, and similarly the two that showed a drop after adrenal medullectomy showed an additional drop after sympathectomy (Fig. 5).

Effect on Blood Pressure.—There were no consistent effects on blood pressure after either adrenal medullectomy or subsequent bilateral sympathectomy (Fig. 6).

Systemic Peripheral Resistance.—Three animals showed no change in the calculated systemic peripheral resistance after either adrenal medullectomy or subsequent sympathectomy, one animal showed a progressive rise in peripheral resistance after both adrenal medullectomy and sympathectomy, and a final animal showed a progressive fall after both adrenal medullectomy and sympathectomy (Fig. 7).

Pulmonary Vascular Resistance.—No consistent changes were demonstrated in pulmonary vascular resistances. Three animals showed no change, one animal showed a progressive increase in resistance, and the final one a progressive fall in calculated pulmonary resistances (Fig. 8).

The data from which these results are drawn are given in Table I, and some of the results are plotted in the accompanying graphs.

TABLE I

DOG AND (WEIGHT) (KG.)	PERIOD	CARDIAC OUTPUT	BLOOD PRESSURE	RIGHT VENTRICULAR PRESSURE	SYSTEMIC RESISTANCE	PULMONARY RESISTANCE	TOTAL OXYGEN CONSUMPTION
1	Control	1520	155/120	40/0	94	14	50.5
(9.5)		1320					46.5
	Postmedullectomy	952					
		860	160/118	38/0	155	22	70.5
							63.0
	Postmedullectomy and sympathectomy	1280	140/90	38/0	119	19	60
		973					56.6
		770					
2	Control	995	180/130	22/0	110	8	50
(11.5)		1181					51
	Postmedullectomy	990	180/130	24/0	140	9	74
		992					68
		1200					76
	Postmedullectomy and sympathectomy	1320	160/120	20/0	100	7.5	73
		1480					68
3	Control	1482	160/125	38/0	105	13	66
(10.6)		1322					70
	Postmedullectomy	1305	180/140	22/0	97	7	63
		2060					72
	Postmedullectomy and sympathectomy	Died on insertion of cardiac catheter					
4	Control	1140					63
(11.7)		1390	185/145	40/0	122	15	65
		1540					70
	Postmedullectomy	2020	200/125	30/0	98	9	94
		1880					85
		1420					76
	Postmedullectomy and sympathectomy	2030	130/80	?	48	?	62
		2430					64
5	Control	895	150/118	28/0	145	15	50
(10)		952					41
	Postmedullectomy	819	142/120	25/0	195	18	50
		510					34
		772					36
	Postmedullectomy and sympathectomy	193	105/52	40/0	268	66	23
		294					53
		416					42

DISCUSSION

The current literature is replete with attempts to implicate the adrenals in the control of vascular tone and, hence, in the pathogenesis of essential hypertension. Both the adrenal cortex and the adrenal medulla have been implicated, and recently it has even been postulated that the quantitative interrelationships of the cortical and medullary hormones are important. The adrenal cortex is dependent on humoral control for the purpose of adapting its secretion to body requirements. The experiments of Vogt[17] and Long[16] have demonstrated that epinephrine is an agent capable of exciting the adrenal cortex. This excitation is not a direct one, but is mediated through the anterior pituitary gland since epinephrine activates the anterior pituitary gland to elaborate ACTH which in turn stimulates the adrenal cortex to increase the output of adrenal cortical hormones. This, in general, seems to be highly important in the response of the organism to "stress." This phase of the pituitary-adrenal response has been termed the "autonomic" phase by Long,[16] since physiologically the autonomic nervous system controls reflexly the secretion of epinephrine. A clinical counterpart of these experimental conditions might be considered in patients with

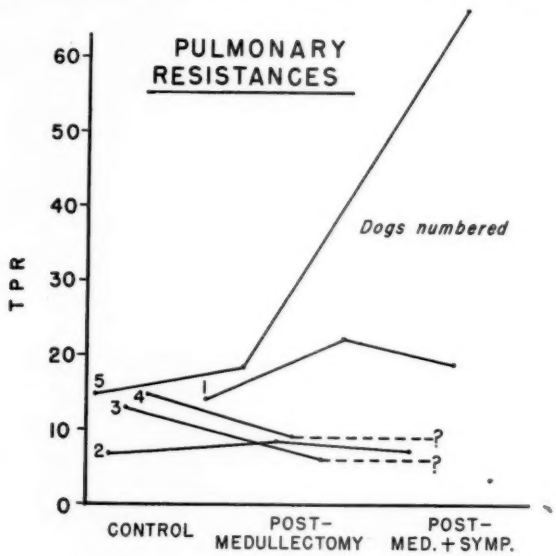

Fig. 8.—Graph showing effects of the procedure on pulmonary vascular resistance.

pheochromocytomas for, interestingly enough, patients with long-standing cases of pheochromocytoma are prone to develop a persistent hypertension, suggesting again a disturbance in vascular tone as a result of prolonged overstimulation of the pituitary gland and adrenal cortex by epinephrine. Epinephrine cannot be directly impugned since its over-all pharmacologic action is to decrease rather than increase total peripheral vascular resistance.[18]

The present study was designed to illustrate the effects of demedullation of the adrenals on peripheral vascular resistance, calculating the latter from measurements of the cardiac output and vascular pressures. Complete adrenal medullectomy was accomplished without injury to the adrenal cortex, as evidenced by microscopic examination of the remaining adrenals, or to the general

status of the animals. No constant effects on peripheral vascular resistance could be demonstrated.

It was conceivable that after demedullation of the adrenals the remaining portions of the sympathetic nervous system, which originate embryologically from the same structures as the adrenal medulla, could serve directly as adrenergic substitutes. The same animals were subjected to rather complete sympathectomy in the hope of eliminating any remaining autonomic phase of pituitary-adrenal cortical excitation. No consistent change in peripheral vascular resistance or cardiac output could be accomplished by combining extensive sympathectomy with adrenal demedullation.

Direct studies of adrenal cortical activity were not made in these animals. It is possible that we interrupted only the autonomic phase of stimulation of the adrenal cortex, and that, in the absence of stress, normal adrenal cortical secretion was occurring through the "metabolic" phase. Long and associates[15] have shown that another very important factor in the elaboration of ACTH by the pituitary gland is the actual level of circulating adrenal cortical hormones within the organism, which again is related to the rate of utilization of adrenal cortical hormones by the tissues. The animals manifested no evidence of adrenal cortical insufficiency. Fluid and electrolyte studies were not felt worth while.

Whatever the factors are that govern vascular tone and reactivity in normal animals they do not seem to be influenced either by adrenal demedullation or extensive sympathectomy, as evidenced by our experiments. The concept of a mechanism mediated through the adrenal medulla and sympathetic nervous system, secondarily activating the anterior pituitary gland and adrenal cortex, may be important in rapid or early adjustments of vascular tone, but in the long-term regulation of peripheral resistance other mechanisms serve the animal admirably. That this mechanism does not seem to lie in the adrenal cortex, or in the metabolic phase of ACTH elaboration, is further clarified by the recent experiments of Turner and Grollman.[19] These authors demonstrated that bilaterally adrenalectomized and nephrectomized dogs, maintained for periods of as long as forty days by means of peritoneal lavage without resort to the use of any hormonal therapy, developed renal hypertension to a degree observed in nephrectomized dogs with intact adrenals similarly lavaged.

On the available experimental evidence sympathectomy, adrenal demedullation, and adrenalectomy seem of dubious rationale in the control of vascular tone.

SUMMARY AND CONCLUSIONS

We have been unable to demonstrate any constant effects of adrenal demedullation alone or in association with extensive sympathectomy on the cardiac output, systemic or pulmonary arterial pressures, or calculated vascular resistances in the normal dog. Whatever the mechanisms are that govern vascular tone and reactivity they are ultimately independent of the adrenal medulla and sympathetic nervous system, as seen from our experiments, and probably from the adrenal cortex, as suggested by others.

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DISCUSSION

DR. KEITH S. GRIMSON (Durham, N. C.).—Dr. Richards has made the important observation that no consistent change of peripheral resistance or of cardiac output is accomplished by combining extensive sympathectomy with adrenal demedullation. This I can confirm because of similar studies, in dogs, of partial sympathectomies, splanchnicectomies, and adrenal demedullation. Other studies in dogs dealt with total sympathectomy. Even without demedullation this procedure, which includes removal of the stellate ganglia with its nerve supply to the heart and to thoracic and cerebral viscera, moderately reduces cardiac output in dogs and man. Dr. Richards did not remove the stellate and second or third thoracic ganglia in his experiments. Therefore, he accomplished splanchnicectomy rather than total sympathectomy, and variable effects upon cardiac output would be expected.

In dog and in man it makes little difference, physiologically, whether a splanchnicectomy is extended upward to remove the seventh or sixth or third thoracic ganglia. Only when the stellate ganglion is removed along with the splanchnic area does decrease of heart rate to fifty or sixty beats per minute and satisfactory block of sympathetic and adrenal vasopressor mechanisms occur. Only then, in my opinion, will there be excellent and lasting effects in patients with hypertension.

METASTASIS FROM MAMMARY CARCINOMA TO THE SUPRACLAVICULAR AND INTERNAL MAMMARY LYMPH NODES

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RADICAL mastectomy is a valuable therapeutic weapon that today is to some degree in disrepute because it has been used indiscriminately, often upon patients whose disease was entirely beyond the reach of the surgeon. The disappointing results obtained with the operation under these circumstances have led surgeons to perform it carelessly. Bad selection of cases is added to bad surgical technique, with disastrous consequences to the patients.

Over a period of years at the Columbia-Presbyterian Medical Center we have attempted to improve our treatment of breast carcinoma by seeking ever more precise clinical criteria which would enable us to select for radical mastectomy only the patients who have some chance of cure. The others have been treated by irradiation. The *criteria of operability* which we published a decade ago were based upon careful evaluation of the clinical picture of the local disease, *clinical* evidence of its regional extension to the supraclavicular and mediastinal regions, and radiographic evidence of its spread to lungs and bones. These criteria have been tested and found useful not only in our own Clinic but in various hospitals in the country and abroad (Tomlinson and Eckert,[1] Wells,[2] and Dahl-Iversen and Soerensen[3]).

Although these criteria have served to exclude a proportion of the cases in which the disease has spread beyond the scope of surgical attack, we have been aware that an important weakness of our criteria has been the lack of a reliable method for determining the existence of regional lymph node metastases. The findings of Andreassen and Dahl-Iversen[4] in their series of supraclavicular lymph node dissections, and Handley's[5] biopsy study of the internal mammary lymph nodes suggested to us a biopsy method for obtaining pathologic proof of the status of the regional lymph nodes. We wish to report our early results with this biopsy method. By substituting pathologic for clinical evidence of the regional lymph node spread of the disease, our criteria of operability gain greatly in exactitude and critical value.

SUPRACLAVICULAR LYMPH NODE METASTASES

Halsted[6, 7] was the pioneer in appreciating the frequency of supraclavicular lymph node metastases and in attacking them surgically. In the early 1890's he began to perform supraclavicular dissection as part of his radical mastectomy.

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Experience had taught him that there was a great likelihood of supraclavicular metastases when the highest axillary nodes were involved. By 1905 he was performing the supraclavicular operation "in most cases." In 1907, when he reported his end results before the American Surgical Association, he had performed the supraclavicular operation in a total of 101 cases primarily and in 18 secondarily. In 44 of these patients the nodes in the neck had been found to be involved, yet only 2 of the 44 had been cured for five years or more.

The poor results of supraclavicular dissection led Halsted's pupils to abandon it. It added a good deal of work to an operation which Halsted himself characterized as "a very great labor," and the number of added cures attributable to it was very small.

During the last twenty-five years our knowledge of the clinical course of breast carcinoma and the results of operation have been improved as a result of the accumulation of long-term follow-up data in a number of clinics. These data again emphasize the importance of supraclavicular metastases. Thus, in our data from the Presbyterian Hospital, 21.8 per cent of the patients who were treated by radical mastectomy between the years 1915 and 1934 and who were found to have axillary metastases later developed clinical evidence of supraclavicular metastases. In these patients the metastases had no doubt already reached the supraclavicular area at the time of operation, but the surgeon had no way of detecting their presence.

It was such data as these which recently led Andreassen and Dahl-Iversen[4] to begin again to perform supraclavicular lymph node dissections supplementing radical mastectomy. During 1947 they performed 98 of these dissections and reported that *33 per cent of the patients who had metastases to the axillary lymph nodes were found also to have occult supraclavicular lymph node metastases.* The supraclavicular metastases were not palpable preoperatively in any of the patients.

The full significance of these findings can only be appreciated in the light of the anatomy of the lymphatic routes to the supraclavicular nodes. There are two main routes for metastasis from the primary focus of carcinoma in the breast to the supraclavicular lymph nodes—the axillary route and the internal mammary route. These routes are illustrated diagrammatically in Fig. 1.

The main route is, of course, through the axillary lymph nodes. There are five main groups of these nodes which serve as a series of filters through which emboli of carcinoma cells escaping from the primary focus of the disease in the breast must pass. The main collecting trunk lymphatics run upward along the lateral aspect of the breast to reach the scapular and central groups of axillary lymph nodes. From these groups of nodes trunk lymphatics run medially to the highest group of axillary nodes—the subclavicular group. This important group of nodes is situated upon and caudad to the axillary vein just before it passes medially beneath the clavicle. Cancer emboli reaching the subclavicular nodes through this main axillary route must pass through several lymph node filters, that is, through a comparatively good protective filtration

system which often catches emboli before they reach the subclavicular group of nodes.

There are, unfortunately, two other groups of collecting trunk lymphatics from the upper portion of the breast which go more directly to the subclavicular nodes. The *interpectoral* collecting lymphatics, after rounding the free edge of the pectoralis major muscle, run upward and medially to an inconstant interpectoral (Rotter's) node or nodes lying between the pectoralis major and minor muscles, and thence directly to the subclavicular group of nodes. The *transpectoral* collecting lymphatics follow the pectoral branches of the thoracoacromial vessels through the pectoralis major muscle and go directly to the subclavicular group of nodes.

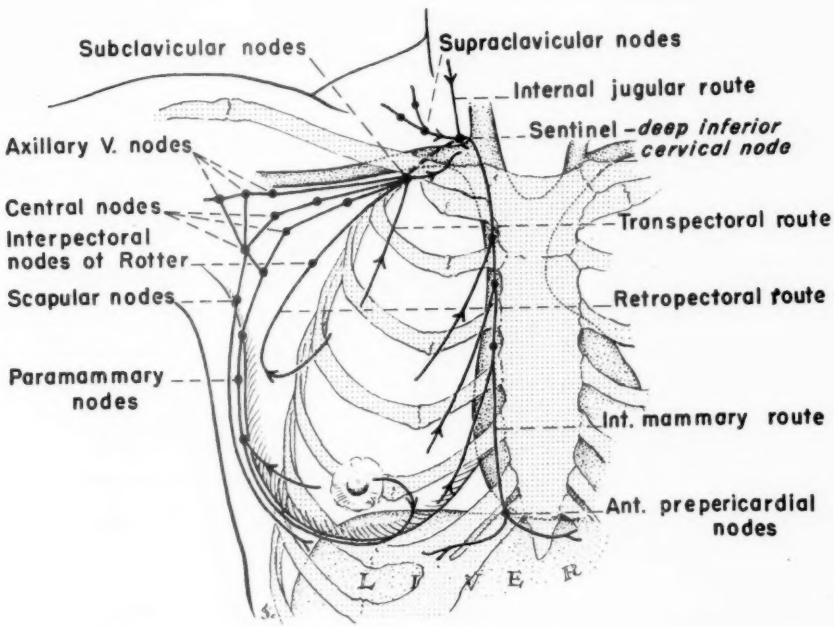

Fig. 1.—Diagram showing the principal lymphatic drainage routes of the breast. The comparative complexity of the axillary and internal mammary routes is evident. The proximity of the highest subclavicular nodes of the axillary lymphatic route, and of the internal mammary node in the first interspace, to the grand central lymphatic terminus at the base of the neck at the confluence of the internal jugular and subclavian veins has great clinical significance.

Experience has taught us that when metastases have reached the subclavicular group of lymph nodes operation never achieves cure. The anatomy of the lymphatics in this region provides a clear explanation for this fact. The details of the anatomy have been worked out comparatively recently by Rodrigues and Pereira[8] in Rouviere's Parisian laboratory. From the subclavicular nodes one or two trunk lymphatics pass upward beneath the clavicle parallel to the subclavian vein to reach the *grand central lymphatic terminus* at the confluence of the internal jugular and subclavian veins. Here these trunk lymphatics empty into the venous stream, either separately or together, with other trunk lymphatics coming from the neck and mediastinum. Just before these trunk lymphatics from the axilla empty into the blood stream they often pass

through a final sentinel inferior deep cervical lymph node lying upon the confluence of the internal jugular and subclavian veins. This sentinel node, when considerably enlarged, can be palpated behind the lateral edge of the attachment of the sternocleidomastoid muscle to the clavicle. The distance between the subclavicular nodes and this sentinel node is but 2 or 3 cm. Experience has taught us that when metastases have reached the subclavicular lymph nodes at the apex of the axilla, the disease has reached the closely adjacent grand central lymphatic terminus and has entered the venous stream or lodged in the sentinel supraclavicular node.

When other supraclavicular lymph nodes are involved by metastases, the process is a retrograde one from the sentinel inferior deep cervical node or nodes. The disease grows backward along the lymphatics to reach more peripherally situated nodes above the clavicle. When such involved supraclavicular lymph nodes are palpated, it should be assumed that the disease has already reached the grand central lymphatic terminus. There is no direct pathway across the clavicle from axillary lymph nodes to supraclavicular lymph nodes, except in very advanced local disease where the skin in this region is involved and the skin lymphatics carry it in all directions.

Metastases can also reach the supraclavicular lymph nodes from the internal mammary route. On each side of the base of the neck the internal mammary lymphatic trunk also empties into the grand central lymphatic terminus at the confluence of the internal jugular and subclavian veins. The termination may be directly into the venous stream or into the sentinel inferior deep cervical node at the venous confluence. It is thus possible to have metastatic involvement of the supraclavicular lymph nodes without axillary lymph node involvement. This is unusual, however, because the internal mammary lymph nodes, to which we must next turn our attention, are ordinarily involved only secondarily, after the axillary lymph nodes become involved.

INTERNAL MAMMARY LYMPH NODE METASTASES

Although the fact that the internal mammary lymphatic route drained the breast was well enough known to be mentioned in the eighteenth edition of Gray's Anatomy in 1910, it has received comparatively little attention from anatomists and surgeons. Even in the twenty-fifth (1948) edition of this famous reference work, the internal mammary nodes are not well described, and there is no adequate illustration depicting them.

Halsted[7] was the first to attack this drainage route surgically. In 1898 he wrote: "Dr. H. W. Cushing, my house surgeon, has in three instances cleaned out the anterior mediastinum on one side for recurrent cancer. It is likely, I think, that we shall in the near future remove the mediastinal contents at some of our primary operations." Halsted never mentioned the matter again. What deterred him we can only guess.

The next surgeon to occupy himself with the problem of the internal mammary route was W. S. Handley.[5] His comprehensive studies of the routes of spread of breast carcinoma carried on during the early years of the century at the Middlesex Hospital, London, convinced him of the importance of the internal

mammary route. In the early 1920's he excised the internal mammary nodes in five patients, but abandoned the procedure "because it makes the operation too long and severe." He treated a series of patients with radium tubes inserted in the intercostal spaces, a method which has not been accepted. He traced the spread of breast carcinoma to the internal mammary nodes in several striking cases, and he reached, in 1927, the important conclusion: "I believe that by the time the axillary glands are enlarged, the disease has frequently, and perhaps usually, obtained access through the inner ends of the intercostal spaces to the internal mammary glands, and that in quite early and still operable cases these glands contain microscopic deposits of cancer cells."

His son, R. S. Handley,[9] has recently added greatly to our knowledge of the internal mammary lymphatic route, and by his brilliant work has stimulated new interest in the problems which metastases to these lymph nodes present. In 1947 he began to search the second intercostal space for lymph nodes. He did this as a biopsy procedure at the completion of radical mastectomy. He learned how to find a lymph node in almost every case, a task requiring much patience and a meticulous technique. He proved his father's thesis that a surprising proportion of these nodes contain metastases. As of July, 1952, he had removed internal mammary nodes in 125 patients.* Metastases were found in 34 per cent.

As his father had predicted, R. S. Handley found that internal mammary metastases are much more frequent when the axillary lymph nodes are involved. The following table from his data shows this relationship.

TABLE I. HANDLEY'S DATA REGARDING METASTASIS TO INTERNAL MAMMARY LYMPH NODE IN CARCINOMA OF BREAST

STATUS OF AXILLARY NODES	NUMBER OF CASES	NUMBER OF INTERNAL MAMMARY METASTASES	PER CENT WITH INTERNAL MAMMARY METASTASES
No metastases	44	4	9
Metastases	81	39	48
Total	125	43	34

The situation of the tumor in the breast also has a relationship to the frequency of internal mammary metastases. Table II shows that these metastases are more frequent when the tumor is in the center of inner one-half of the breast.

Dahl-Iversen[3] in Copenhagen, in 1951, reported a biopsy study of the internal mammary nodes in the first, second, and third interspaces in a series of fifty-three clinically operable cases (Haagensen and Stout criteria[10, 11]) of

TABLE II. HANDLEY'S DATA REGARDING METASTASES TO INTERNAL MAMMARY LYMPH NODE IN CARCINOMA OF BREAST WITH AXILLARY METASTASES

SITUATION OF TUMOR	NUMBER OF CASES	NUMBER OF INTERNAL MAMMARY METASTASIS	PER CENT WITH INTERNAL MAMMARY METASTASIS
Inner one-half	35	26	74
Outer one-half	46	13	28
Total	81	39	48

*Personal communication.

breast carcinoma. Like Handley, he performed these biopsies at the end of standard radical mastectomy. He found nodes in one or more of these three interspaces in 43 of his patients. Metastases were demonstrated in these nodes in 10 of the patients. The incidence of proved internal mammary metastases in the series of 53 cases was therefore only 19 per cent. The series as a whole was made up of unusually favorable cases, however, as indicated by an incidence of only 47 per cent of axillary lymph node metastases.

Margottini,[12] in Rome, began to resect the internal mammary lymphatic chain en bloc as part of his radical mastectomy in 1948. His technique included removal of 2 cm. of the second and third costal cartilages, and the block dissection of the internal mammary vessels with surrounding fat and lymph nodes, ligating the artery and veins as low down as possible in the third space, and as high as possible in the first space. Margottini's operation is therapeutic in purpose, unlike Handley's biopsy of the second intercostal space which seeks information only.

By July, 1950, Margottini had performed his operation upon a total of 227 patients. He summarized his findings as follows:

> The internal mammary lymph nodes were found invaded in about 5 per cent of cases of carcinoma of the breast, when the tumour was small and there were no axillary metastases. When these were present the incidence of parasternal metastases rose to 27.7 per cent for tumours of the external quadrants, and to 40.5 per cent for those of the inner quadrants. If the tumour occupies the greater part of the breast the mammary nodes are invaded in over 50 per cent of cases.

More recently, Urban,[13, 14] in New York, has begun to include block resection of the internal mammary chain as part of his radical mastectomy. In his technique the sternum is split, permitting resection of a trap door of chest-wall tissues, including portions of the second, third, fourth, and fifth costal cartilages. The continuity of this trap door and the internal mammary chain which lies upon its deep surface, with the mastectomy specimen as a whole, is preserved. Urban began to perform this operation in 1951. As of July, 1952, he had performed it in 57 patients. He selected patients whose primary carcinomas were situated in the median one-half of the breast. In 20 of these 57 patients neither axillary nor internal mammary metastases were found. Of the 33 patients who had axillary metastases 24, or 73 per cent, were found to have internal mammary metastases. Four patients who had no axillary metastases were found to have internal mammary metastases.

The findings in these early attempts at surgical attack upon the internal mammary lymphatic route should be interpreted in the light of our knowledge of the anatomy of this route and the pathology of the metastatic process in it. The collecting lymphatics of the internal mammary route drain the central and medial portions of the breast. They follow the perforating blood vessels, which provide a great part of the blood supply of the breast, down through the pectoralis major muscle, to empty into the nodes of the internal mammary chain. These nodes are concentrated in the upper three interspaces. W. S. Handley stimulated an English anatomist, E. P. Stibbe, to make the first comprehensive

study of the internal mammary lymphatic route. In a series of 60 post-mortem examinations Stibbe[15] found the average total number of nodes per subject to be 8.5. The typical distribution was four on one side and five on the other, with one node in the upper three spaces on each side, one in the sixth space on each side, and an extra node in one of the upper spaces on one side.

The nodes lie in the fatty areolar tissue upon the endothoracic fascia, and in the plane of, or superficial to, the plane of the internal mammary artery and veins, beneath the internal intercostal muscle.

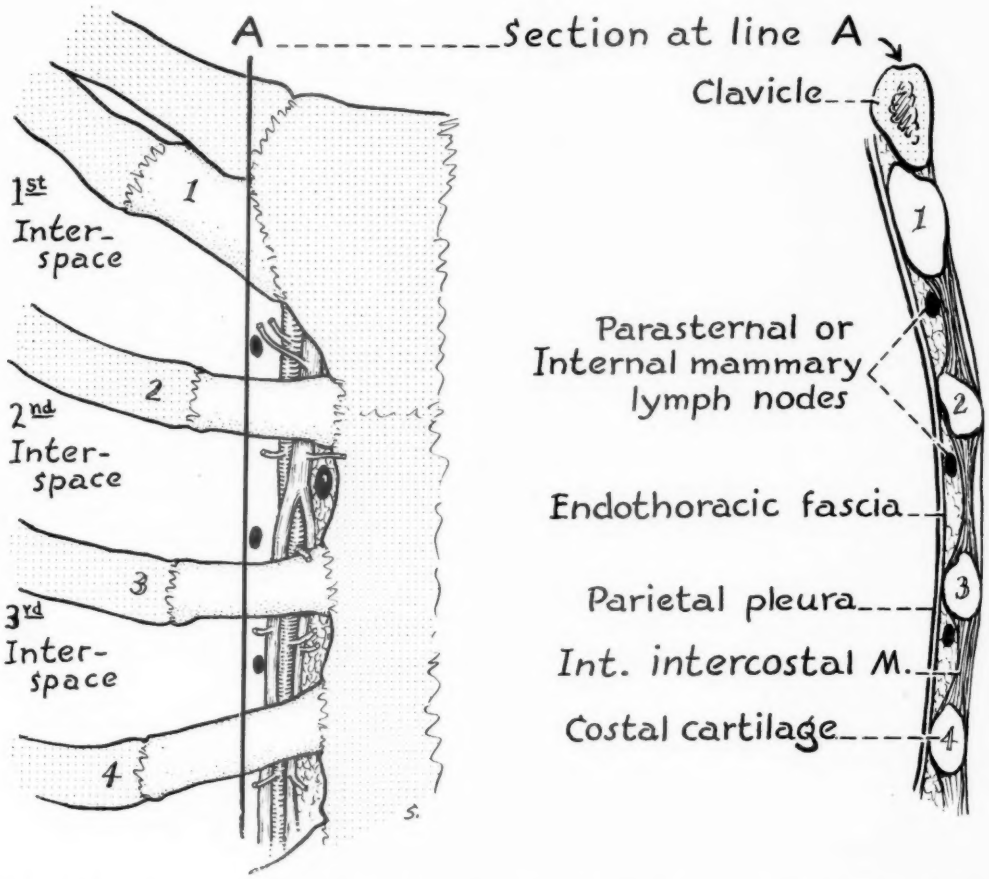

Fig. 2.—Frontal and sagittal views of the upper three intercostal spaces showing the relations of the internal mammary lymph nodes.

The nodes are situated in the interspaces between the costal cartilages, within 3 cm. of the edge of the sternum. The firm attachment of the endothoracic fascia to the deep surfaces of the costal cartilages and the sternum normally prevents the nodes from lying behind the costal cartilages and sternum, but they may lie partially concealed in the groove at the edge of the cartilage, as Soerensen has pictured them.

Soerensen's[3] study was made in 1951 at the suggestion of his Copenhagen surgical colleagues. It was based upon 39 autopsy examinations. He found

an average total of 7 nodes per subject, or 3.5 on each side. Soerensen's diagram of the positions of these nodes in the several interspaces gave a very good impression of their location and size.

Soerensen emphasizes a fact which is of fundamental importance in a consideration of these internal mammary nodes—namely, their minute size. He points out that the great majority of the normal nodes are only 1 or 2 mm. in diameter, with a few measuring as much as 5 or 6 mm. in diameter. They are, in fact, so small that they cannot be identified and removed by a surgeon who is not possessed of a meticulous technique and small instruments which enable him to keep the small operative field dry of blood and to see the nodes. Often when a node cannot be identified and the fat adjacent to the internal mammary vessels is removed, microscopic study will show in it one or more minute aggregations of lymphoid tissue, not large enough to be recognized grossly.

At the Francis Delafield Hospital, during the last two years, a study of the internal mammary nodes in a series of 100 autopsy specimens from patients dying of neoplastic disease has been made by Ju and his associates. The sternums and attached costal cartilages were removed in one piece and the internal mammary nodes subsequently dissected out and examined microscopically.

The distribution of internal mammary nodes in relation to the vessels in this study is summarized in Fig. 3 which compares this data with that published by Stibbe in 1918.[15] In contrast to Stibbe's series which showed a marked concentration of nodes in the first three spaces and at the bifurcation of the vessels in the fifth and sixth spaces, Ju[19] noted a more even distribution with a gradual diminution in node concentration in the lower interspaces. This is in agreement with Soerensen's findings.[3]

In 9 out of 13 patients dying with breast carcinoma, metastatic tumor was found in the internal mammary nodes, and in most of these instances the involvement was bilateral. Table III summarizes the findings in the 100 autopsy specimens examined.

TABLE III. PRIMARY SITE OF CANCERS WITH INTERNAL MAMMARY NODE METASTASES

	NUMBER OF CASES	NUMBER WITH POSITIVE INTERNAL MAMMARY NODES	PER CENT WITH POSITIVE INTERNAL MAMMARY NODES
Lymphomas	13	6	46.1
Thoracic lesions	32	17	51.1
Breast	13	9	69.2
Lungs	13	6	46.1
Other	6	2	33.3
Head and neck	15	3	20.0
Gastrointestinal area	21	4	19.1
Kidney, bladder, prostate, and penis	8	3	37.5
Female genital tract	9	3	33.3

It will be noted that the patients dying from breast carcinoma had the highest incidence (69.2 per cent) of positive internal mammary nodes. One should not overlook the fact, however, that some 30.8 per cent of the patients in this group died from disseminated breast cancer without involvement of the internal mammary lymph nodes.

Nodes containing metastases were usually at least 4 or 5 mm. in diameter. It is noteworthy, however, that even at the end stage of disseminated carcinoma, with massive metastases in the viscera elsewhere, the involved internal mammary lymph nodes remained only from 1 to 2 cm. in diameter. The disease had presumably been present in the internal mammary region for a long time, yet it had not grown to sufficiently massive proportions to give any clinical or radiographic evidence of its presence in this region.

The significance of metastasis in these internal mammary lymph nodes is related to the origin and termination of this lymphatic route. The internal mammary lymphatic trunks originate from lymph nodes lying upon the upper surface of the diaphragm which Rouviere calls "anterior prepericardial" nodes. These nodes receive collecting trunks from the anterior portion of the diaphragm, and from the anterior and superior surfaces of the liver via the round ligament, as well as from that portion of the anterior abdominal wall supplied by the superior epigastric artery.

Emboli of carcinoma cells from the breast usually go first to the axillary nodes, even when the primary tumor is situated in the central or inner one-half of the breast. The axillary route is the main route of the lymphatic drainage from the entire breast. The best proof of this is provided by small carcinomas of the medial edge of the breast, of which we have seen several, which metastasized first to the axillary nodes. As the disease grows in the axillary node filters it chokes them and impedes the flow of lymph through this route. There is then an increasing tendency for deviation of the lymphatic flow carrying emboli of carcinoma cells toward the secondary internal mammary route. This tendency is greater when the primary tumor is situated in the central and medial portions of the breast, as Handley's[16] data clearly show. In one of our patients, however, a comparatively small tumor of the lower outer sector of the breast, which had produced good-sized axillary metastases, had also metastasized to the second internal mammary node.

When emboli lodge in one or more of the upper three internal mammary nodes, the biopsy data which we so far have available suggest that it is the node in the second intercostal space which is most often involved. It must be kept in mind, however, that these data are prejudiced by the fact that the second interspace is more easily explored than the first or third, because it is wider, and that for this reason nodes have been more often recovered from it. We greatly need more information concerning the condition of all upper three internal mammary nodes at an early stage of metastatic involvement of this lymphatic route.

We do know that these internal mammary nodes are a poor filter, an inferior barrier, to the escape of carcinoma emboli as compared with the axillary lymph nodes. There are only 3, or in some subjects 4, very small internal mammary nodes strung out along a single lymphatic trunk, while in the axilla there are from 40 to 60 lymph nodes, a number of them of good size, in a complex network of lymphatic trunks.

When the internal mammary route is blocked by metastases in the nodes the disease extends along its collecting trunk, either cephalad or caudad, or

sometimes in both directions. If the spread is caudad, the process is one of retrograde permeation. In this direction the disease soon reaches the liver. We have unfortunately observed the progression of breast carcinoma along this route to the liver in a number of our patients.

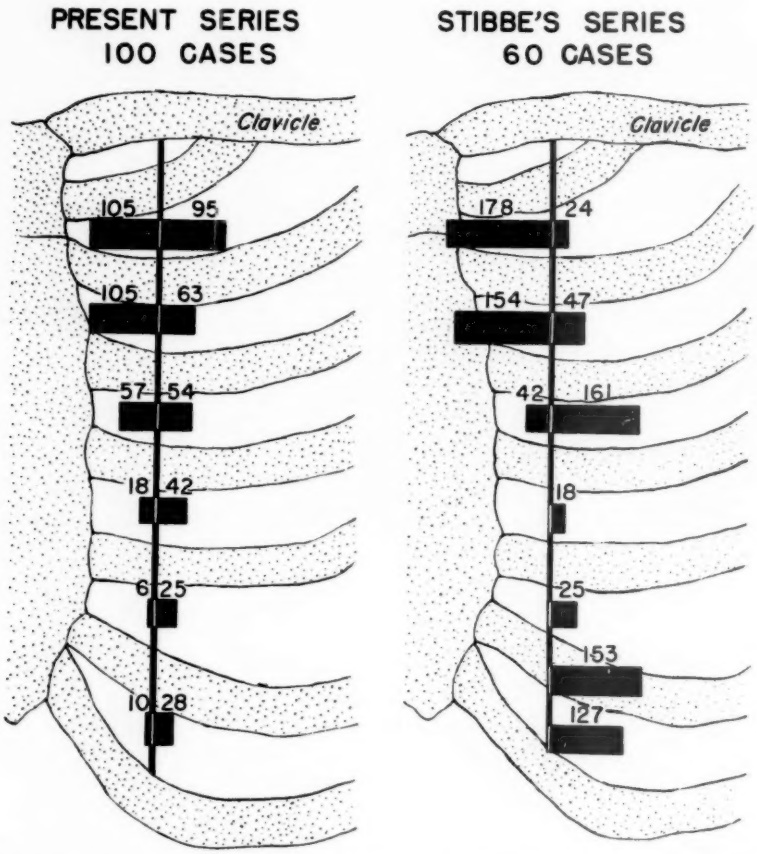

Fig. 3.—Graphic representation of the number and position of internal mammary lymph nodes found by Ju and his associates compared with the report of Stibbe. The diagram shows frequency of internal mammary nodes in relation to the internal mammary artery. Figures represent the total number of nodes recorded in each area per 100 cases.

If the spread is cephalad the process is probably at first embolic. The internal mammary lymphatic trunk, on each side, runs cephalad from the internal mammary node in the first interspace, a distance of only 5 or 6 cm., to enter the grand central lymphatic terminus at the junction of the internal jugular and subclavian veins. Here the trunk terminates either separately or by joining with other lymphatic trunks, such as the internal jugular and the subclavicular, in the sentinel inferior deep cervical lymph node which lies upon the confluence of the internal jugular and subclavian veins. In some subjects the internal mammary trunk empties separately directly into the venous confluence.

When carcinoma emboli from the internal mammary route block the sentinel node at the venous confluence, the disease extends by retrograde lymphatic permeation backward into the supraclavicular nodes.

SUPRACLAVICULAR AND INTERNAL MAMMARY BIOPSIES AS CRITERIA OF OPERABILITY

When we realized, from R. S. Handley's[9] work, the feasibility of excising internal mammary lymph nodes through the intercostal spaces, we got the idea of using the procedure *for biopsy prior to radical mastectomy,* making it a criterion of operability. We began, in 1951, exploring the second interspace

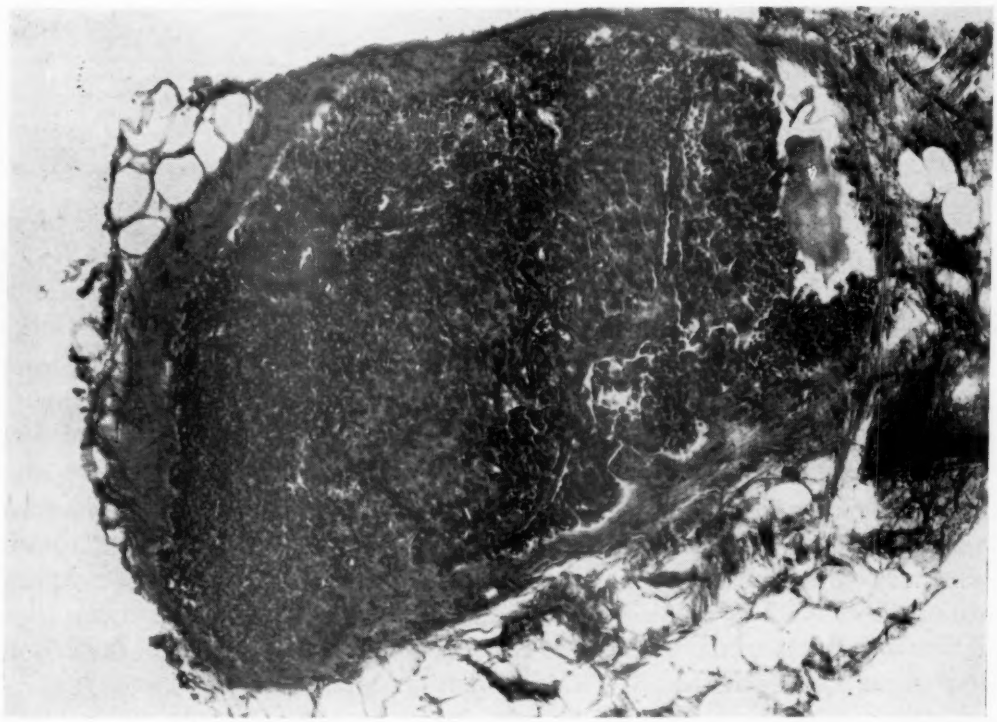

Fig. 4.—Microscopic section showing the entire transverse diameter of a small internal mammary lymph node removed for biopsy from a patient with mammary carcinoma. Metastatic cancer is evident in the marginal sinus on the left as well as throughout the central portion of the node.

with this purpose in mind. We learned to find these small nodes and to do frozen sections upon them. We were surprised to discover by this method, in a number of instances, minute foci of metastatic disease in nodes that were only 3 or 4 mm. in diameter. Fig. 4 shows such a small node containing metastases. The method requires a meticulous surgical and pathologic technique. To illustrate its difficulty we had the experience on one occasion, when we cut a 3 mm. node in half and used one-half for frozen section and saved the other half for permanent section, that the frozen-section half did not contain carcinoma, while the permanent-section half did. In this regard Ackerman[17] is making it a practice to cut many sections from each one of these small internal mammary nodes in order to be certain not to miss minute foci of carcinoma. This is certainly a wise precaution.

We chose for internal mammary biopsy those patients who had clinical evidence of axillary metastases, as well as those whose tumors were in the central or medial portions of the breast. Our data do not at all represent a consecutive series of cases or the results of any one surgeon. Some of the

operators undoubtedly missed positive nodes while becoming familiar with the biopsy technique. For these reasons our series of cases is not strictly comparable with Handley's series.

To date we have data on 104 cases of internal mammary biopsy. These are shown in Table IV.

TABLE IV. INTERNAL MAMMARY LYMPH NODE BIOPSIES

	CENTER AND INNER HALF	OUTER HALF	TOTAL
Number of cases	66	38	104.0
Internal mammary metastases	27	8	35.0
Per cent internal mammary metastases	41	21	33.6

Since only a few of the patients with internal mammary metastases in our series had radical mastectomy we do not know the exact relationship of axillary metastases to internal mammary metastases in our data. We can only presume from the clinical evidence that most of the patients had axillary metastases.

It is important to note that in our series of cases, as in the other series to which we have referred above, the frequency of metastases to the internal mammary nodes is almost twice as high in carcinoma of the center and inner one-half of the breast as it is in carcinoma of the outer one-half of the breast.

As our knowledge of the spread of carcinoma of the breast along the internal mammary route has grown, not only as a result of these biopsies of internal mammary nodes but from our experience with block dissection of the internal mammary chain in a number of cases, we have come to realize that metastases in the internal mammary nodes is usually a sign of widespread involvement of regional lymph nodes. We have become convinced of the necessity, in certain types of cases of doubtful operability, of biopsying not only the internal mammary nodes in the second interspace, but the nodes in the first and third interspaces as well, and of biopsying the nodes in the region of the grand central lymphatic terminus at the base of the neck. Dahl-Iversen's[3] findings with supraclavicular dissection were the final evidence which led us recently to adopt supraclavicular biopsy as another criterion of operability. With this step we placed our estimate of the presence of internal mammary as well as supraclavicular metastases upon a pathologic rather than a clinical basis. We have substituted facts for conjecture. Our criteria of operability have become, we believe, considerably more dependable.

This involves performing in some cases what we call a *triple biopsy,* preliminary to decision as to treatment. This is done under general anesthesia. The first step is an incision biopsy of the primary tumor in the breast. Through a small incision directly over it we excise a 5 mm. wedge of the tumor. We do not excise the whole tumor for biopsy unless it is very small, that is, 1 cm. or less in diameter. The wound is not cauterized, but after careful hemostasis, it is closed with interrupted sutures of silk. Since we know that a biopsy wound of this type will leak serum and blood containing carcinoma cells, we seal it over with rubber cement and rubber dam, to make sure that we will not transplant carcinoma cells into the next two biopsy sites.

The second step is biopsy of the internal mammary nodes in the upper three intercostal spaces. Through an incision parallel with the edge of the sternum we search for nodes in the second, third, and first spaces, in the order named. We often explore the second intercostal space first because it is the easiest interspace in which to find a node, and if we find one which contains metastasis and wish to discontinue further search we may do so. It is desirable to explore all three interspaces whenever possible because in some cases involved nodes have been found in the first or third interspace although none was found in the second interspace.

The third step in our triple biopsy is a supraclavicular dissection. Following the technique of Dahl-Iversen a transverse incision across the base of the neck is used. The sternomastoid muscle is retracted medially and the internal jugular vein is cleared down to the grand central lymphatic terminus at its confluence with the subclavian vein. All of the lymph node-bearing tissue in the triangle bounded by the internal jugular vein, the subclavian vein, and the posterior belly of the omohyoid muscle is then excised in one block. From three to twelve nodes are usually found in this block of tissue.

This kind of thorough triple biopsy is obviously not justified in all patients with breast carcinoma. It necessitates an additional separate operative procedure, for it requires two or three hours to complete, and it is too much for both patient and surgeon to add this to the "very great labor," to use Halsted's phrase, of the radical mastectomy as we perform it. We carry out radical mastectomy, if the internal mammary and supraclavicular nodes prove not to contain metastases, a week after triple biopsy. We believe that triple biopsy is indicated in all patients in whom there is clinical evidence of axillary metastases. It is also indicated for large tumors of the center of the breast, and for tumors of the inner one-half of the breast, because these are likely to have metastasized to the internal mammary nodes. It should also be performed, we believe, in all cases in which the extent of the local disease in the breast makes operability doubtful.

In 8 of the 13 cases in which we have so far performed the triple biopsy, metastases have been found in both the supraclavicular and internal mammary lymph nodes. Fig. 5 shows the findings in one of these cases in which triple biopsy provided proof of inoperability. In the 5 other cases in which triple biopsy was performed metastases were not found in either the supraclavicular or internal mammary lymph nodes. Fig. 6 shows the findings in 1 of these 5 cases in which the negative findings correctly encouraged us to proceed with radical mastectomy. The results of triple biopsy in this small series of cases suggest a correlation between internal mammary and supraclavicular lymph node metastases, in patients with axillary metastases. If this correlation is borne out in a larger group of cases, it will have an important bearing on the selection of cases for a more radical type of operative attack upon breast carcinoma currently being advocated by Wangensteen,[18] by Margottini,[12] and by Urban.[13]

Wangensteen[18] has been combining radical mastectomy with dissection of the supraclavicular as well as of the anterior mediastinal regions in continuity.

If the disease has not reached the grand central lymphatic terminus at the confluence of the internal jugular and subclavian veins, this operation is unnecessarily radical. If metastases have reached this critical point, it seems highly probable to us that the disease has already invaded the blood stream and operation will be futile. If this be true, Wangensteen's procedure will exact an increased morbidity without any compensating increase in cure rate.

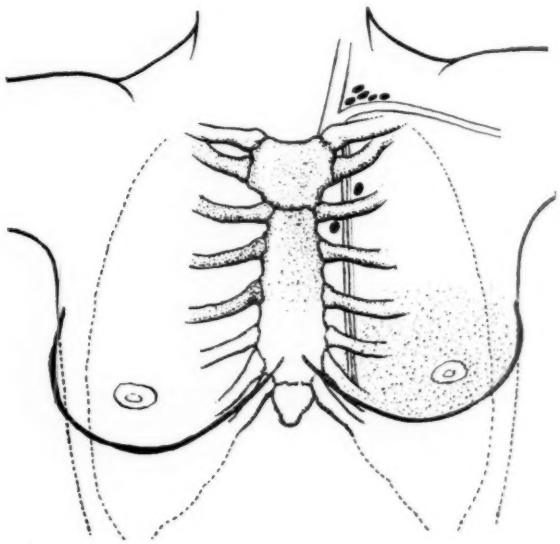

Fig. 5.—Diagrammatic drawing of Mrs. V. D. (Case No. 2103), a 29-year-old housewife, who had noted a lump in the left lower breast for two years. Her local physician had examined her repeatedly during this time, but had advised no treatment. During the last eight weeks the skin of the breast had become edematous and red in color. No lymph nodes were palpable in the axillary or supraclavicular regions. On Dec. 21, 1952, a "triple biopsy" was performed. The breast lesion was a carcinoma infiltrating the dermal lymphatics. Five lymph nodes obtained from the supraclavicular region as well as one node each from the first and second interspaces all contained metastatic carcinoma. Although this patient was categorically inoperable by the criteria of Haagensen and Stout, the biopsies served to document this classification.

The evaluation of block dissection of the internal mammary chain is more difficult. The various techniques for such a dissection as a separate step, as well as for block dissection combined with radical mastectomy, must be viewed from the practical standpoint of what price the patient pays in terms of added morbidity and mortality, and what gain there is, if any, in terms of eradication of the disease. Long-term survival and cure rates, even when they become available, will not provide an easy answer to the last question. There are too many variables. The most important of these is the fact that case series differ too much as to the extent of disease in the cases which make them up, to expect a significant difference in cure rates as a result of comparatively minor changes in therapy.

For the moment we can justify internal mammary block dissection only by the facts of pathology. We already know enough about the extension of breast carcinoma in these regional lymph node areas to state that *block dissection of the internal mammary lymph node chain is unjustifiable unless preliminary biopsy study of the supraclavicular lymph nodes has shown them not to be involved.*

They often contain metastases when the disease has reached the internal mammary nodes, and block dissection of the latter is then, of course, futile.

It is equally true that *block dissection of the internal mammary chain is unjustified unless it has been proved by preliminary biopsy of the internal mammary region in the first interspace that the disease has not reached this vital point.* We have learned this from careful microscopic study of the small series of block dissections of the internal mammary chain that have been carried out in the Presbyterian Hospital, as well as from studies of the anatomy of the

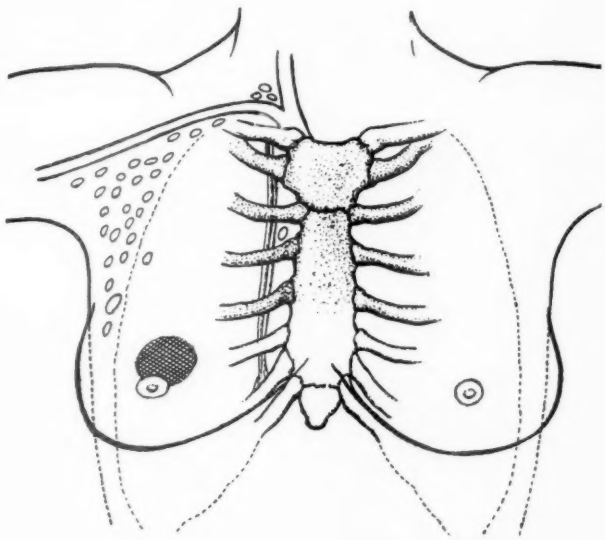

Fig. 6.—Diagrammatic drawing of Mrs. B. B. (Case No. 1654), a 38-year-old housewife, who presented a 4 by 5 cm. mass in the upper inner quadrant of the right breast associated with one firm node in the right axilla. A preliminary "triple biopsy" on June 5, 1952, showed the breast tumor to be an undifferentiated carcinoma, but lymph nodes from the second intercostal space and supraclavicular region contained no metastatic tumor. A subsequent radical mastectomy yielded twenty-seven axillary nodes, none of which contained tumor. The preliminary biopsies in this instance suggested a relatively good prognosis. A block resection of the internal mammary lymph node chain in such an instance would seem unnecessarily radical treatment.

lymphatics in this region. In 7 specimens of block dissections that we have studied in which metastases were found in the internal mammary nodes, there was microscopic disease in the tissues of the first interspace close to the margin of the block in 5 (Fig. 7). The first interspace is a very narrow one, and a surgeon can have no reasonable hope of getting beyond the limits of the disease if it has reached this point and his line of dissection goes through this interspace. Another hazard, when metastases have reached the first interspace, is that at this level there is a cross communication with the internal mammary chain on the other side. Our autopsy studies showed both sides to be often involved.

The node in the first interspace is only about 6 or 7 cm. from the grand central lymphatic terminus at the confluence of internal jugular and subclavian veins where metastases enter the blood stream. When metastases are found in the first interspace we believe that hope of cure by surgery is gone, just as when metastases are found in the highest subclavicular axillary nodes. These are both *points of no return* in the surgical attack upon carcinoma of the breast.

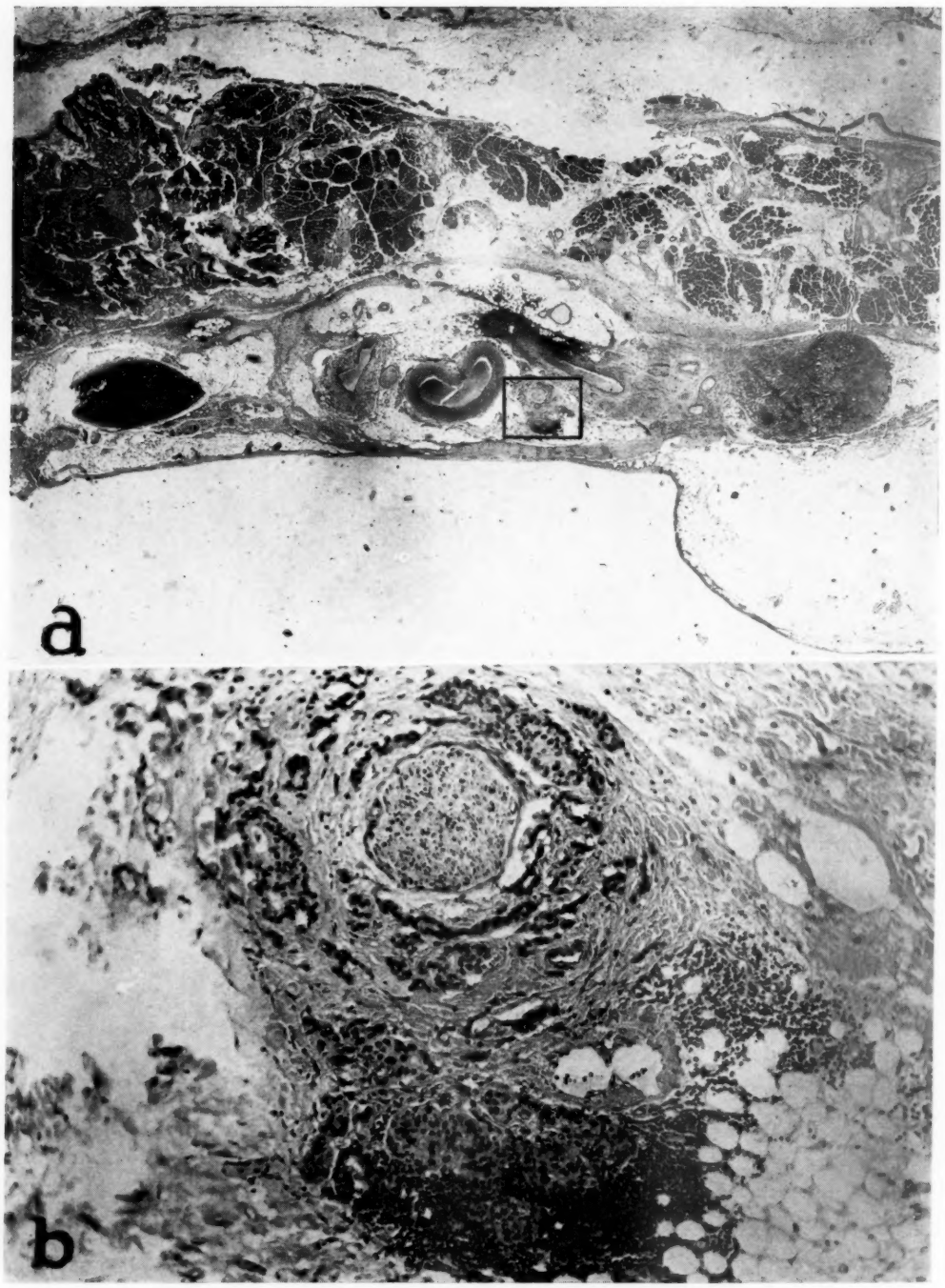

Fig. 7.—*a*, Low-power section through an intercostal space from a block resection of the internal mammary region performed for mammary carcinoma. The internal mammary vessels are evident near the center of the photograph with the pleural surface between them and the intercostal musculature above. The darkly stained object on the left is a lymph node which appears normal at this magnification while on the far right is another lymph node largely replaced by metastatic carcinoma.

b, A high-power magnification of the small boxed area from *a*. In the upper central portion there is a nerve trunk surrounded by lymphatic spaces which are clogged with tumor cells. In the inferior portion of the photograph a miscroscopic aggregate of lymphoid tissue is also heavily infiltrated with metastatic tumor.

It should be kept in mind that the anatomy of the region in which the internal mammary nodes lie is not favorable for surgical attack upon carcinoma in them. These nodes are confined, as we have pointed out, in a narrow space directly upon the endothoracic fascia and pleura. When carcinoma emboli lodge in one of these small nodes, and grow through its capsule into the areolar tissue in which the nodes lie, the disease is too near the limits of the surgeon's block dissection for much hope of cure. Fig. 7, *a* and *b* illustrates this situation in a transverse section through such a specimen from a block dissection. In Fig. 7, *a* the structures lying in areolar tissue close to the pleura, at the lower edge of the specimen in the microphotograph, are, from left to right, an uninvolved internal mammary node, an internal mammary vein, the internal mammary artery, a small nerve infiltrated by carcinoma (marked by a square), another internal mammary vein, and finally another internal mammary node from which carcinoma has grown into the surrounding areolar tissue. Fig. 7, *b* shows in higher power the area marked by the square. The perineural lymphatics of the nerve are extensively involved by carcinoma, and a small unencapsulated focus of lymphocytes situated close to the nerve also contains carcinoma. We can hope to cure, by block dissection, only carcinoma that has reached the internal mammary region at an earlier stage of the disease process than that illustrated by these photomicrographs. The carcinoma must be confined within the lymph nodes, and the nodes as well as the other tissues in the first interspace must not be involved.

The policy of excising the internal mammary nodes for biopsy to determine the advisability of internal mammary block dissection, encounters certain difficulties in its practical application. It would seem unwise, for example, to excise for biopsy involved nodes in the second or third interspace in patients in whom the other factors relating to the extent of the carcinoma appear to justify subsequent internal mammary block dissection. In his biopsy excision of an involved node in such a case the operator might implant carcinoma in skin or other tissues which would not be removed in the subsequent block dissection. We have attempted to solve this dilemma by classifying our patients with breast carcinoma into two groups—those in whom internal mammary block dissection is for one reason or another not to be considered, and those in whom it might have some value. The following are some facts upon which this distinction is based:

CLINICAL FEATURES	INTERNAL MAMMARY DISSECTION
Carcinoma locally inoperable according to Haagensen-Stout criteria	0
Supraclavicular biopsy positive	0
General condition of patient contradicts internal mammary dissection	0
Carcinoma of medial or central portion of breast	+
Carcinoma of lateral portion of breast	0
No enlargement of axillary node	0
Enlarged axillary nodes	+

In the patients in whom internal mammary block dissection is not to be considered, the internal mammary biopsy procedure is begun in the second interspace and continued to the third and first interspaces in the order named. An involved node found in any of these interspaces is sufficient to rule out further surgery.

In the patients in whom internal mammary block dissection is being considered the first interspace only is biopsied. If the tissues obtained from it show no carcinoma, internal mammary block dissection may have some justification.

In the patients in whom the supraclavicular and first interspace internal mammary nodes are proved by biopsy not to be involved, and it has been decided to add internal mammary block dissection to radical mastectomy, a final question remains to be answered: Is it wise to carry out the operative attack in one stage, maintaining the continuity of the breast with the sector of chest wall being excised, or is it preferable to carry out the radical mastectomy and internal mammary block dissection in separate stages? In favor of the latter plan is the fact that in patients with carcinoma of the medial one-half of the breast the amount of skin and subcutaneous tissue over this area which should be sacrificed is so great that covering over the defect in the underlying chest wall consequent to the internal mammary block dissection requires a considerable plastic procedure shifting the opposite breast medially. The internal mammary dissection adds about two hours of operating time to an operation that takes us at least five hours to perform, and the opening of the thoracic cavity in the internal mammary dissection adds an element of shock and postoperative morbidity. All of this penalizes the patient, and no compromise as to the extent of the operation is possible, for it is certainly not justifiable to curtail the thoroughness of the removal of tissues on the chest wall, and thereby to jeopardize our chances of eradication of the local disease, in exchange for the questionable gain which may come from block dissection of the internal mammary chain. There is less of a temptation to curtail the thoroughness of the radical mastectomy if it is performed as a separate first stage and the internal mammary block dissection is carried out later as a second stage. The objection that such staging sacrifices removal in continuity of the lymphatic pathways from the breast to the internal mammary nodes may not prove to be a valid one. It may be argued that metastasis to internal mammary lymph nodes takes place at first by embolism, leaving the collecting lymphatics running from the breast to these nodes uninvolved. Permeation of these lymphatics probably occurs only at a late stage in which any surgical attack is futile. A definite advantage of performing the radical mastectomy only as a first stage is that the study of the axillary lymph nodes in the operative specimen makes it possible to know with certainty whether or not they contain metastases. This fact has a vital bearing on the probability of internal mammary metastases and the rationale of internal mammary block dissection.

Patients in whom breast carcinoma is deemed inoperable should be treated by radiation. Modern intensive protracted radiation has great palliative value in the disease. Biopsy proof of the existence of the disease in the supraclavicular or internal mammary regions enables the radiotherapist to direct his radiation more exactly to these regions, and to improve his results.

SUMMARY

The use of supraclavicular and internal mammary lymph node biopsy for determination of the extent of regional lymph node metastases in carcinoma of

the breast has increased the exactitude of our criteria of operability for the disease and has avoided much futile surgery.

Our criteria in their present form follow:

BREAST CARCINOMA IS INOPERABLE

1. When extensive edema of the skin over the breast (more than one-third of the skin area) is present.

2. When satellite nodules are present in the skin over the breast.

3. When the carcinoma is the inflammatory type.

4. When any two, or more, of the following signs of locally advanced carcinoma are present:

a. Ulceration of the skin.

b. Edema of the skin of limited extent (less than one-third of the skin over the breast).

c. Fixation of the tumor to the chest wall.

d. Axillary lymph nodes measuring 2.5 cm. or more, in transverse diameter.

e. Fixation of axillary lymph nodes to the skin or the deep structures of the axilla.

5. When there is edema of the arm.

6. When, in patients with clinically involved axillary lymph nodes, a supraclavicular dissection reveals metastasis in the supraclavicular lymph nodes.

7. When, in patients with clinically involved axillary lymph nodes, biopsy of the internal mammary lymph nodes reveals metastasis.

8. When roentgenographic study of the skeleton reveals metastases, or when the patient has a history of recently developing pain in the back or pelvic region suggesting metastases.

9. When roentgenographic study of the lungs reveals metastases.

10. When palpation of the liver suggests that it contains metastases.

There is need for more detailed knowledge of the pathology of the regional extension of carcinoma of the breast in the supraclavicular and internal mammary regions. It may be justifiable, in the light of what we already know, to carry out block dissections of the internal mammary chain in certain types of cases, but this should be done only when the supraclavicular region, as well as the internal mammary region in the first intercostal space, has been proved by biopsy to be free of carcinoma. Cases fulfilling these conditions are few. We must not uselessly penalize a large proportion of our patients with this trying disease by subjecting them to indiscriminate internal mammary block dissection that can hope to benefit only a few.

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DISCUSSION

DR. S. J. STABINS (Buffalo, N. Y.).—This paper is particularly interesting to me, as it is no doubt to everyone else here. In 1942 Dr. Dowdy and myself reported on 193 cases of carcinoma of the breast followed at the Strong Memorial Hospital. At that time we reported our over-all, five-year survival rate in those patients with axillary metastasis. The five-year survival in the outer quadrant tumors with axillary metastasis was 35.7 per cent, whereas in those patients with carcinoma of the breast in the inner quadrant, 8.3 per cent were alive five years later. I believe this point is important in the light of what has been said this morning.

DR. HENRY T. RANDALL (New York, N. Y.).—I would like to congratulate Dr. McDonald on a perfectly beautiful exposition, and also perhaps offer a slightly different point of view. We have had experience now with pathologic examination, following en bloc internal mammary chain resection combined with radical mastectomy as described by Urban in 81 patients.

(Slide.) You see here the breast divided into seven sections. The inner half of the breast is divided into four parts, A and B superiorly and C and D inferiorly, while the subareolar area is marked E and the lateral half superiorly F and inferiorly G. You will notice that there is a much higher incidence of internal mammary node metastases in patients whose primary lesions were in areas A and C, the most medial sections, but that internal mammary chain nodes may be involved by a lesion anywhere in the breast, although the incidence is much less from F and G.

Now I think that the point I would like to make in the brief time I should talk is this: That there were four cases, 5 per cent of the series, in which only internal mammary nodes were involved, 23 per cent in which only the axillary nodes were involved, and 36 per cent in which both were involved.

These patients were selected only to the extent of having largely inner quadrant or subareolar lesions, and to the extent of not being categorically inoperable. We did not attempt to perform the operation on some of the more advanced types of patients, such as a few that Dr. McDonald showed.

It is entirely too early to say whether or not inclusion of this second major route of lymphatic spread is going to improve results in radical mastectomy. If the patients are not medically marginal in their operability, the morbidity of this procedure is relatively low. Good chest-wall stabilization can be obtained by fascia lata graft, and perhaps some other synthetic material will be better.

There has been one death in this series, and that was from a cerebrovascular accident approximately three days postoperatively.

We have to wait, of course, and it will probably be five years from now before I may be able to report to you what this series will show in comparison with others. But certainly, if there are nodes involved in the internal mammary chain, and particularly involved nodes in the internal mammary chain in the absence of high axillary metastases, I think that this procedure does offer in selected cases a hope for survival that the standard radical mastectomy does not offer at the present time.

DR. DANELY P. SLAUGHTER (Chicago, Ill.).—I think this problem is an important one but, obviously, it cannot be settled at the present time. It will take three or four more years before there is any evidence as to increase in five years' survival free of disease. Nevertheless, I think it is fair to state that if cancer is left in the internal mammary chain, radiation will not handle it in an adequate percentage to make it a reasonable treatment. Our own experience is minor compared with what has been recorded here. We have seventeen patients in whom we deliberately picked medial quadrant lesions, in whose treatment we have combined internal mammary chain resections; twelve of these have positively internal mammary nodes, and in two of these patients the axilla was negative.

At present, my philosophy in the use of this operation is that it will probably add little, if anything, in the advanced case, because I think we have little chance of curing that patient. Its best use will likely be in the very early case with a medial quadrant lesion, where only one or two nodes may be involved, and in that situation I think it may be a lifesaving procedure. I think it may be; I do not know.

I would like to know why the presence of an internal mammary node makes a breast patient categorically inoperable, too, by the way.

DR. EDWIN ALONZO LAWRENCE (Indianapolis, Ind.).—It has been interesting to me also to observe the contrasting developments in the use of this procedure. I have a different thought, however, that I should like to present to you to the effect that in this day and age when we have made so much progress in so many fields of surgery it is most distressing that this operation should even be considered. In other words, I believe that the presence of metastases in both the axillary and internal mammary chains of nodes at the time when the patient comes to definitive therapy represents a failure of preventive medicine. Furthermore, it seems to me that when the primary tumor has sufficient growth potential to send metastases to these two areas the ultimate salvage rate will not be greatly increased by the combined resection of internal mammary as well as the axillary nodes, for I believe that at this time microscopic tumor is probably present in other parts of the body.

DR. McDONALD (Closing).—In reference to the definition of inoperability, one can state categorically that internal mammary node involvement renders a patient inoperable for the customary type of radical mastectomy. Whether the more radical procedures, which included resection of the sternum, will salvage any significant number of these patients is the question now being put to a clinical test.

Our data indicate that it is illogical to use the more radical procedures without a preliminary supraclavicular biopsy because of the high incidence of concomitant involvement

of supraclavicular and internal mammary nodes. The sternal resections are not likely to be of value, either, in cases where tumor has reached the first intercostal space.

It should be stressed that the internal mammary chain of three or four nodes is a very meager filter when compared with the axilla which contains from thirty to sixty lymph nodes, or the neck from which we often recover as many as 100 nodes in our cleared specimens. Furthermore, the internal mammary chain does not drain the breast in tandem since there are direct drainage routes into each of the interspaces.

It is relevant factual anatomic and clinical evidence such as we have presented that leads us to be pessimistic about the value of more radical operations for carcinoma of the breast. We feel a clinical test of these procedures is justified in special clinics suitably equipped to evaluate them, but a more precise definition of the criteria for using the more radical operations is needed, and our work is a step in that direction.

CLINICAL AND METABOLIC STUDIES OF BILATERAL ADRENALECTOMY FOR ADVANCED CANCER IN MAN

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BILATERAL adrenalectomy has been performed in 33 patients with advanced cancer in the period from February, 1951, to November, 1952. Twelve of these patients had advanced prostate cancer, 12 had advanced breast cancer, and 9 had various other inoperable tumors. The rationale of this experimental study and the preliminary results have been previously reported by us.[1] In brief, this procedure was undertaken in the attempt to remove a potential source of androgen, estrogen, and other steroids which might be influential in maintaining the growth of certain human neoplasms. For this reason our interest has been concentrated on patients with advanced prostrate or breast carcinoma who had previously been gonadectomized. This report presents our further experience with this procedure.

In all instances bilateral adrenalectomy was performed in one stage, usually through bilateral lumbar incisions. The patients were maintained during the operative and postoperative periods with the use of cortisone or hydrocortisone as the only hormonal replacement therapy. The details of the maintenance regime have been published.[2] Our patients, with rare exceptions, have withstood this arduous surgical procedure well, and those patients whose general condition permitted it have been able to perform their normal activities in an unrestricted manner with oral cortisone or hydrocortisone for life maintenance.

In 1945, Huggins and Scott[3] performed bilateral adrenalectomy in 4 patients with advanced prostate cancer who were in relapse following castration and estrogen therapy. This initial attempt was unsuccessful because of a lack of adequate, life-maintaining, hormonal replacement therapy. In 1951, Huggins and Bergenstal[4, 5] published preliminary reports of the effects of bilateral adrenalectomy in patients with advanced prostate and breast cancer using cortisone and desoxycorticosterone for life maintenance. They reported clinical improvement in 5 of 7 patients with prostate cancer and improvement in one man with breast cancer. In 1952, Huggins and Ling-Yuan Dao[6] presented their results in 7 patients with advanced breast cancer. Objective improvement was apparently obtained in 5 of the 7 patients. In 3 patients who improved, surgical castration was performed shortly before, shortly after,

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*Damon Runyon Senior Clinical and Research Fellow.

or simultaneously with adrenalectomy, so that it is difficult to determine whether the improvement should be ascribed to castration, to adrenalectomy, or to both. In 2 of the patients who improved, adrenalectomy alone was performed.

Harrison and his co-workers[7] have also reported their experience with adrenalectomy in 7 patients with advanced prostate cancer. Clinical improvement was noted in 6 of the 7 patients. All of their patients had previously been orchidectomized and had received estrogen therapy. All of their patients continued to receive estrogen therapy as well as desoxycorticosterone and cortisone during the postadrenalectomy period. Nine patients were treated with cortisone without adrenalectomy and 8 patients obtained some relief of symptoms.

RESULTS

Prostate Cancer.—The results of adrenalectomy in 12 patients with prostate cancer are presented in Table I. The response is divided into subjective and objective improvement. Subjective improvement means relief of the most prominent presenting symptom, which was, most commonly, pain. Objective improvement refers to regression in the size of tumor masses measured either by direct palpation or from x-ray changes. All but 2 patients (F. M. and M. C.) had been orchidectomized months to years prior to adrenalectomy. Every patient had received estrogen therapy prior to adrenalectomy.

TABLE I. RESULTS OF ADRENALECTOMY IN PROSTATE CANCER

PATIENT	LENGTH OF SURVIVAL (DAYS)	DURATION OF IMPROVEMENT		PRESENT STATUS	CAUSE OF DEATH
		SUBJECTIVE (DAYS)	OBJECTIVE (DAYS)		
L. M.	2	0	0	Dead	Cerebral hemorrhage
R. G.	11	0	0	Dead	Cancer
F. M.	21	0	0	Dead	Myocardial infarction
F. H.	33	21	0	Dead	Cancer
N. T.	81	81	0	Living	
M. B.	124	30	0	Dead	Cancer
I. B.	128	90		Dead	Adrenal insufficiency
T. H.	133	30	133	Dead	Unknown (? Adrenal insufficiency)
W. S.	196	150	0	Dead	Cancer
A. B.	201	60	0	Dead	Cancer
J. W.	294	220	0	Dead	Cancer
M. C.	351	14	0	Living	Castrated 5 weeks after adrenalectomy

Only one patient demonstrated objective regression of tumor masses following adrenalectomy. This man (T. H.) had a large mass arising from the prostate which nearly occluded the rectum and, in addition, there were hard masses palpable in both lower quadrants of the abdomen. Six weeks following adrenalectomy, all observers agreed that there had been definite shrinkage of the tumor masses. He died 133 days after adrenalectomy at an outside hospital of an obscure cause, which we have assumed to be adrenal insufficiency. Autopsy revealed only three minute tumor masses, one in the

prostate gland and one each at the junction of the ureters with the bladder. That marked shrinkage of prostatic carcinoma occurred as a result of adrenalectomy in this patient appears to be unequivocal.

Five patients had symptomatic improvement lasting from two to seven months. The clinical improvement in these patients was striking and appeared to indicate that adrenalectomy had induced some alteration in the growth of prostatic neoplasms. Despite the marked clinical improvement, however, the prostatic metastases continued to grow as evidenced by progressive changes in the skeletal radiographs, and there was a gradual exacerbation of symptoms. There was no significant fall in the serum acid phosphatase levels following adrenalectomy in any patient. The discrepancy between symptomatic and objective improvement in these patients is difficult to evaluate, but it would appear that adrenalectomy brought about some subtle change in the course of the neoplastic growth which accounts for the clinical improvement.

Two patients failed to show any significant improvement following adrenalectomy.

Three patients survived adrenalectomy for too short a period for adequate evaluation. In one patient, adrenalectomy was carried out prior to castration. No improvement occurred in this patient. Orchidectomy performed five weeks after adrenalectomy produced a prompt clinical remission.

It may be concluded from these results that adrenalectomy, as presently carried out, does not offer a practical form of therapy for patients with advanced prostatic carcinoma. From the experimental viewpoint, however, the results obtained in 6 of our patients, and the results reported by Harrison and associates,[7] suggest that certain adrenal cortical steroids may be of importance in maintaining the growth of prostatic carcinoma. Possible inadequacies of the present regime for adrenalectomy present themselves.

Graham[8] has found accessory adrenal cortical tissue in the region of the celiac plexus in 32 per cent of 100 consecutive autopsies at Memorial Hospital. These accessory glands averaged 7 by 4 by 3 mm. in size and the histology was similar to that found in the usual adrenal gland. Thus, bilateral adrenalectomy probably does not constitute total adrenalectomy in many patients. The administration of cortisone should suppress the function of this tissue, but the degree of suppression of normal adrenal cortical tissue by this means is not known. Withdrawal of cortisone in 7 of our adrenalectomized patients resulted in the prompt development of acute adrenal insufficiency, indicating that if accessory adrenal tissue was present in these patients its function was inadequate for life maintenance. In one adrenalectomized patient, cortisone withdrawal failed to induce abrupt clinical collapse, and over a six-week period a classical clinical picture of Addison's disease developed, suggesting that this patient had some functioning adrenal cortical tissue remaining. Death occurred at a later date; unfortunately, an autopsy was not obtained in this patient. A systematic search for accessory adrenal cortical tissue has not been carried out in our other patients who have come to autopsy. With the probability of failure of surgical adrenalectomy to be

complete in a high percentage of patients, other means of suppressing adrenal function must be sought. It seems probable that hypophysectomy would accomplish this purpose.

It has been impossible in our experience to maintain life in adrenalectomized patients without the use of cortisone or hydrocortisone. Desoxycorticosterone and salt have been singularly ineffective for life maintenance in man in contrast to their usefulness in adrenalectomized animals. Cortisone and hydrocortisone are metabolized in man into at least one end product which has androgenic properties. This metabolite is 11-OH-androsterone.[9] Thus, if androgen is important in maintaining the growth of prostatic carcinoma in man, then adrenalectomy with maintenance on cortisone or hydrocortisone has not succeeded in eliminating androgen from these patients. Recently, some of us[10] have demonstrated that corticosterone is capable of maintaining life in a bilaterally adrenalectomized patient. Corticosterone does not appear to be metabolized into the usual neutral 17-ketosteroids, and it seems possible that its metabolites may not have androgenic properties. Further study of bilateral adrenalectomy for advanced prostate cancer in man with the use of corticosterone for life maintenance is being pursued.

Breast Carcinoma.—The results of adrenalectomy in 12 women with advanced breast cancer are shown in Table II. The same criteria for evaluating subjective and objective responses were used as in the patients with prostate cancer. In addition, in those patients who had progressive osteolytic metastases, calcium balance studies were used as an objective index of alteration in tumor growth.[11, 12] All of these patients had surgical castration at least six weeks prior to adrenalectomy, and the clinical response to oophorectomy was carefully evaluated (see Table III).

TABLE II. RESULTS OF ADRENALECTOMY IN BREAST CANCER

PATIENT	LENGTH OF SURVIVAL (DAYS)	DURATION OF IMPROVEMENT		PRESENT STATUS	CAUSE OF DEATH
		SUBJECTIVE (DAYS)	OBJECTIVE (DAYS)		
P. K.	18	0	0	Dead	Cancer and bronchopneumonia
R. G.	74	0	0	Dead	Cancer
R. L.	100	30	0*	Dead	Cancer
A. C.	119	14	0	Dead	Cancer
S. B.	121	60	0*	Dead	Cancer
M. D.	170	21	0	Dead	Cancer
G. B.	84	0	0	Living	Improved with androgen
L. K.	228	120	120	Dead	Cancer
V. Y.	264	264	264	Living	—
G. M.	368	120	120	Living	Transient remission with androgen
M. L.	88	88	88	Living	—
B. M.	82	82	82	Living	—

*Regression of skin and bone metastases with simultaneous progression of liver metastases.

Patients who improved: Five of the 12 patients with mammary cancer have had subjective and objective remissions induced by adrenalectomy. One patient is still in remission nine months after adrenalectomy. Two patients

had remissions which lasted for four months followed by relapse. Two patients are in remission approximately three months after adrenalectomy.

The regression of tumor masses in Patient V. Y. is illustrated in Fig. 1. The sequence of events in this patient is as follows: right radical mastectomy

Fig. 1.—Patient V. Y. Photographs showing regression of mammary carcinoma. Adrenalectomy was performed on May 12, 1952. *A*, May 7, 1952; *B*, Jan. 21, 1953; *C*, May 7, 1952; and *D*, Jan. 1, 1953.

was performed approximately one and one-half years prior to adrenalectomy for infiltrating duct carcinoma, Grade II, with metastases to the axillary lymph nodes. X-ray castration was carried out at the time of mastectomy because of the poor prognosis. Local recurrence of the tumor in the chest wall

was first noted one year prior to adrenalectomy. X-ray therapy to the local lesions was given eight months prior to adrenalectomy. Testosterone in an average dose of 300 mg. per week was given more or less continuously from nine months to twelve days prior to adrenalectomy with steady progression of tumor growth during this period. Oophorectomy was performed fifty-one days prior to adrenalectomy while testosterone administration was continued. Progressive growth of the skin lesions was noted until adrenalectomy was performed. Regression of the skin tumors first became apparent one month after adrenalectomy. At nine months postadrenalectomy, there is only one minute tumor nodule that remains palpable. Biopsies of the skin continue to show scattered and apparently unaltered carcinoma cells. Although it is conceivable that the lesions may have responded unfavorably to the testosterone, and that withdrawal of this hormone twelve days prior to adrenalectomy may have had a role in inducing the observed tumor regression, it seems more likely that adrenalectomy was responsible for this major therapeutic achievement.

The objective evidence for inhibition of tumor growth in the 4 other patients who improved following adrenalectomy is based primarily on changes in calcium metabolism. The only demonstrable lesions in these patients were osteolytic metastases, with the exception of two small skin nodules in Patient G. M. and a small palpable mass in the remaining breast of Patient B. M. The calcium balance data on Patient G. M. are presented in Fig. 2. During an eighteen-day period prior to adrenalectomy, there was a marked hypercalciuria while the patient received a low calcium intake. Under these conditions, hypercalciuria is indicative of bone destruction and is considered to reflect the rate of growth of the osteolytic tumor. Immediately after adrenalectomy, there was a sharp drop in urinary calcium excretion and, subsequently, calcium balance became markedly positive when the calcium intake was increased. These findings are indicative of inhibition of the osteolytic process and active osseous deposition of calcium. The rise in serum alkaline phosphatase levels following adrenalectomy is also consistent with an increased osteoblastic activity. Urinary calcium excretion remained within normal limits for four months after adrenalectomy. X-ray surveys of the skeleton during this period revealed no significant changes. Two subcutaneous metastases in this patient decreased in size to the extent that they could no longer be palpated at the end of six weeks after adrenalectomy and no new lesions have appeared. There was a return of back pain four months after adrenalectomy, and at six months hypercalciuria was again present.

The data obtained in Patient L. K. are similar to those just described for G. M. Relapse occurred four months after adrenalectomy. As discussed earlier, this patient failed to develop acute adrenal insufficiency when maintenance cortisone was withdrawn, suggesting that adrenalectomy was not complete. It is of interest to speculate whether the short duration of the remission might be related to this.

Patient M. L. had hypercalcemia for six weeks prior to adrenalectomy. Hypercalcemia disappeared within a few days after adrenalectomy and hyper-

calciuria gradually subsided. Urinary calcium excretion was normal two and one-half months postadrenalectomy and x-ray pictures of the skeleton showed no change in the bony metastases.

Patient B. M. showed a sharp decrease in urinary calcium excretion immediately after adrenalectomy, and the urinary calcium remained within low normal range two months later. X-ray examination of the skeleton two months after adrenalectomy showed no definite change. The tumor mass in the breast has not changed significantly in size.

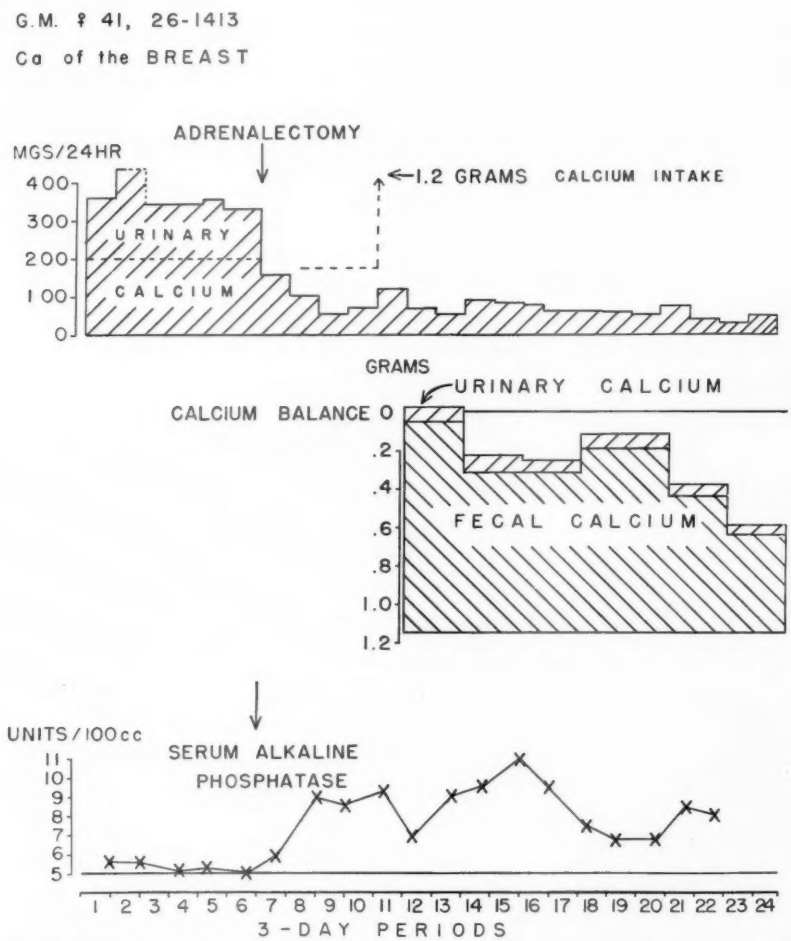

Fig. 2.—Calcium excretion studies. ***Calcium balance,*** **The dietary intake is plotted down from the zero line and the fecal and urinary outputs are superimposed on the intake from below, upward.**

Patients who failed to improve: Seven of the 12 patients with breast cancer failed to show significant improvement after adrenalectomy. One patient (P. K.) survived for too short a period to be evaluated. In 3 patients (R. G., A. C., and M. D.) tumor growth continued unabated after adrenalectomy. One patient (G. B.), who had failed to improve symptomatically by one month after adrenalectomy, was given androgen and x-ray therapy to the spine, so that the effect of adrenalectomy cannot be adequately evaluated beyond

this time. Two patients (R. L. and S. B.) showed objective evidence of regression of skin and bone metastases with simultaneous rapid growth of liver metastases. The apparent paradoxical effect of adrenalectomy on the growth of tumor in these 2 patients is difficult to explain.

These results indicate that adrenalectomy induces marked temporary inhibition of the growth of mammary carcinoma in some patients, whereas this procedure is completely without effect on tumor growth in other patients. Adrenalectomy was of prolonged therapeutic value in one patient in this series.

The mechanism by which adrenalectomy induced improvement in these patients is not known. The pathologic diagnosis of the tumor tissue in all of the patients with mammary tumors was infiltrating duct carcinoma, Grade II or III. The pathologic sections* of both the primary and metastatic lesions in these patients have been reviewed and nothing has been found to suggest reasons for regarding any of these tumors. The clinical data in this group of patients have presented no clues as to why some patients responded and others did not.

It appears reasonable to postulate that, in the patients who responded favorably, adrenalectomy eliminated some steroid produced by the adrenal cortex which was contributing to the maintenance of growth of the tumor. Recent observations by some of us[13] indicate that the favorable response obtained from oophorectomy in some patients with mammary carcinoma is due to the removal of ovarian estrogens. As a working hypothesis, we have assumed that estrogen is the steroid which is eliminated or greatly reduced

TABLE III. RESPONSE OF PATIENTS WITH BREAST CARCINOMA TO ANDROGEN, CASTRATION, AND ADRENALECTOMY

PATIENT	AGE (YR.)	TIME OF ONSET* OF DISEASE	TIME* OF ADMINISTRATION OF ANDROGEN	RESPONSE TO ADMINISTRATION OF ANDROGEN	TIME* OF CASTRATION	RESPONSE TO CASTRATION	RESPONSE TO ADRENALECTOMY
G. M.	41	5 yr., 7 mo.	27 to 17 mo.	+	14.5 mo.	+	+
L. K.	50	5 yr.	19 to 13 mo.	+	10.5 mo.	+	+
M. L.	52	2 yr., 2 mo.			7 mo.	+	+
V. Y.	44	2 yr., 10 mo.	8 mo. to 12 days	0	18 mo.	P†	+
B. M.	49	5 yr., 7 mo.	23 to 2 mo.	+	3 yr., 11 mo.	P†	+
S. B.	41	2 yr., 7 mo.			7 mo.	+	0‡
R. L.	45	9 yr., 10 mo.	24 to 15 mo.	0	9 yr.	P†	0‡
A. C.	24	1 yr., 5 mo.	5 to 2 mo.	0	7 mo.	0	0
M. D.	54	1 yr., 2 mo.			47 days	0	0
R. G.	47	3 yr., 1 mo.			46 days	0	0
G. B.	42	5 yr., 2 mo.			3 yr., 4 mo.	P†	0

*Prior to adrenalectomy.

†Prophylactic.

‡Regression of skin and bone metastases with simultaneous progression of liver metastases.

*Reviewed by Dr. Frank Foote.

in amount by adrenalectomy. With this hypothesis in mind, we have tried to correlate the clinical response to surgical castration with the response to adrenalectomy. The data are presented in Table III.

It will be noted that, of the 5 patients who responded to adrenalectomy, 3 responded favorably to oophorectomy and in 2 prophylactic castration was performed. Of the 6 who failed to respond to adrenalectomy, 3 failed to respond to surgical castration, in 2 prophylactic castration was performed, and 1 responded to oophorectomy. The latter patient showed regression of skin and bone lesions with simultaneous progression of liver metastases following adrenalectomy and for this reason was considered not to have responded. It is obvious that there are insufficient data from which to draw conclusions, but it will be of interest to determine whether this trend is borne out by further observations.

Miscellaneous Tumors.—Bilateral adrenalectomy was performed in 9 patients with seven different types of tumors. The results are listed in Table IV. No significant alteration in tumor growth could be discerned in these patients as a result of adrenalectomy.

TABLE IV. EFFECT OF ADRENALECTOMY IN VARIOUS ADVANCED NEOPLASMS

PATIENT	DIAGNOSIS	LENGTH OF SURVIVAL (DAYS)	DURATION OF IMPROVEMENT		STATUS	CAUSE OF DEATH
			SUBJECTIVE (DAYS)	OBJECTIVE (DAYS)		
R. E.	Ca cervix	52	12	0	Dead	Cancer
B. K.	Ca cervix	131	30	0	Dead	Cancer
E. S.	Ca endometrium	32	0	0	Dead	Cancer
F. D.	Ca endometrium	184	0	0	Dead	Postoperative radical surgery, perforated duodenal ulcer, peritonitis
H. S.	Ca ovary	75	30	0	Dead	Cancer
A. B.	Leiomyosarcoma of uterus	167	0	0	Dead	Cancer
A. L.	Acute leukemia	48	0	0	Dead	Cerebral hemorrhage
J. L.	Malignant melanoma	31	10	0	Dead	Cancer
J. W.	Adenocarcinoma of cecum	59	0	0	Dead	Cancer

Metabolic Studies.—The physiologic effects of bilateral adrenalectomy in man and the details for maintenance of these patients have been published.[2] Further observations on the alterations in water and salt metabolism in acute adrenal insufficiency, induced by withdrawal of cortisone from adrenalectomized patients, will be presented in detail elsewhere.[14]

Adrenalectomized patients are well maintained on oral cortisone as the only hormonal replacement therapy. The average maintenance dosage is 50 mg. per day, administered in divided doses of 25 mg. every twelve hours. Some patients do better on 75 mg. per day, given in 25 mg. doses every eight

hours. The cortisone dosage is adjusted to the individual patient on the basis of the symptomatology, namely his sense of well-being, strength, and appetite. There is no single laboratory test which helps to define the eucorticoid state. On this maintenance regime, the patient can withstand moderate stress, such as a twenty-four hour fast or an upper respiratory infection. During a period of more severe stress, however, such as pneumonia or surgery, cortisone replacement must be temporarily increased. In the event that surgery is necessary, the patient should be handled in the same manner as when adrenalectomy is performed. When acute adrenal insufficiency develops, intravenous free cortisone should be administered promptly.

We have withdrawn cortisone from adrenalectomized patients in the attempt to maintain them without any steroid hormone administration. It soon became apparent that this was not possible. When cortisone was withdrawn, clinical collapse developed promptly. Within twenty-four hours of cortisone withdrawal, the patient complained of malaise, lethargy, anorexia, and weakness. At forty-eight hours, the patient noted giddiness in the upright position and such profound weakness that he was unwilling to leave the bed. At seventy-two hours, the patient was usually unable to take food, and nausea, vomiting, diarrhea, and stupor frequently ensued. The blood pressure fell but not to shock levels as long as the patient remained horizontal. The patient developed a gaunt and ashen appearance, the skin was cold and dry, the pulse was weak, and it appeared that death would soon follow. Administration of cortisone at this time brought about dramatic clinical improvement usually within twelve hours, so that the patient was ready to eat and to ambulate, and he felt well.

Studies of water and electrolyte metabolism during cortisone withdrawal were surprising in that the low salt syndrome so classically described in animal experiments and in the Addisonian patient failed to develop in our patients. The changes in serum sodium, sodium balance, urine volume, and body weight during a three-day period of cortisone withdrawal in Patient I. B. are shown in Fig. 3. It can be seen that there was a prompt fall in serum sodium without a loss of salt from the patient when cortisone was withdrawn. The daily urine volume fell sharply and there was a marked gain in body weight. When cortisone was readministered there was a prompt fall in body weight and a rise in urine volume, and the serum sodium returned to a normal level. These findings are indicative of water retention and intoxication during cortisone withdrawal.

Similar changes in water and electrolyte metabolism have been observed in other adrenalectomized patients during cortisone withdrawal, but frank water intoxication was seen in only the one patient discussed previously. In seven withdrawal studies, water retention was the most frequently observed metabolic change. During cortisone withdrawal, urinary sodium loss was conspicuously absent in 4 patients. Significant hyponatremia, which could not be explained by loss of body sodium, developed in 4 patients. Four patients gained weight during cortisone withdrawal. Potassium retention

was not observed in 5 patients on whom these measurements were made. Serum potassium remained normal in 6 patients. Hypoglycemia failed to develop even in the late stages of acute adrenal insufficiency. There was an apparent expansion of the inulin space of 15 to 21 per cent, without significant change in the total body water or total exchangeable body sodium during cortisone withdrawal in the 2 patients so studied. When cortisone was readministered, 6 of the 7 patients promptly lost one to three kilograms of body weight due to water diuresis.

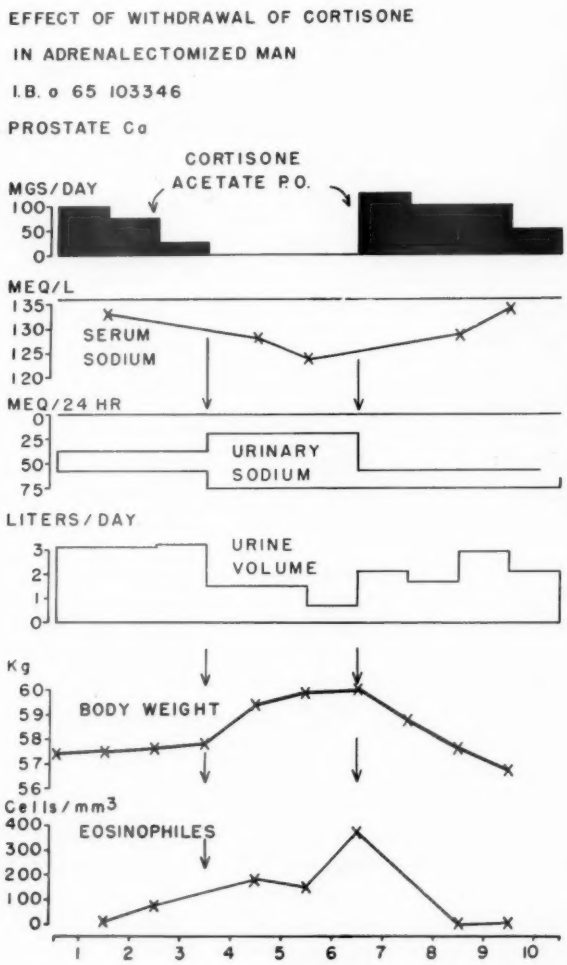

Fig. 3.—Sodium excretion studies. Sodium balance. The sodium intake is plotted down from the zero line and the urinary sodium excretion is superimposed on the intake from below, upward. The sodium balance is positive throughout the study. (From West and associates.[1])

Although internal and external changes in salt and water metabolism have been measured, the results tend to minimize the role of these phenomena in acute adrenal insufficiency in man. The changes in tissue metabolism which instigate the clinical collapse during acute adrenal insufficiency are not delineated by these studies, and they remain obscure.

These results are at variance with experimental data in animals and the classical concepts of the salt-losing Addisonian patient. A brief extrapolation of these results to the clinical management of acute adrenal insufficiency emphasizes the need for individualization of treatment. An agent, such as intravenous free cortisone or free hydrocortisone, which provides rapid adrenal hormone replacement is the crux of treatment in all cases. However, the indiscriminate and vigorous administration of saline solution and water must be weighed against the possibilities of an already expanded extracellular fluid or of water intoxication. In the treatment of hypotension, vasoconstrictors have the first priority, unless there are specific indications to warrant bolstering the blood volume. Administration of 100 mg. of free cortisone* or free hydrocortisone* in 500 c.c. of 5 per cent glucose in water, given by continuous intravenous drip over a four-hour period, will usually bring a patient out of an adrenal crisis in four to six hours.

1. Bilateral adrenalectomy has been performed in 33 patients with advanced cancer in the period from February, 1951, to November, 1952. Twelve patients had advanced prostate cancer, 12 had advanced breast cancer, and 9 had various other inoperable tumors. The patients were maintained with oral cortisone or hydrocortisone as the only hormonal replacement therapy.

2. One patient with prostate cancer showed objective regression of tumor masses following adrenalectomy. Five patients had symptomatic improvement lasting two to seven months after adrenalectomy, but all showed progressive growth of tumor metastases during this period and 4 have died of the cancer. Six patients showed no improvement.

3. Adrenalectomy for advanced prostate cancer as presently carried out is not a practical therapeutic procedure.

4. One patient with advanced mammary cancer has had major therapeutic improvement continuing nine months after adrenalectomy. Four patients have had short clinical remissions following adrenalectomy; 2 of these patients relapsed after four months. Seven patients failed to improve.

5. Oophorectomy was performed in all patients with mammary cancer six weeks or more prior to adrenalectomy, and the clinical response to oophorectomy was carefully evaluated. Present trends suggest that patients who respond favorably to castration are more likely to have a favorable response to adrenalectomy.

6. Further observations are required to determine the possible role of adrenalectomy as practical therapy for advanced mammary cancer in man.

7. Metabolic studies of the effects of withdrawal of cortisone maintenance therapy in adrenalectomized patients are presented. The findings provide a new physiologic concept for the treatment of acute adrenal insufficiency in man.

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*The free cortisone and free hydrocortisone for intravenous use were supplied through the kindness of Dr. Augustus Gibson of Merck and Company, Inc.

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DISCUSSION

DR. WILLIAM D. HOLDEN (Cleveland, Ohio).—These studies of Dr. Pearson and his associates are extremely interesting. We have had an opportunity to make some similar studies, although not quite so many, and in almost every respect we can confirm the observations that have been presented this morning. Our studies have been confined to the metabolic alterations resulting from osteoclastic breast cancer and to a few other diffuse cancers, such as melanosarcomas.

The response to bilateral adrenalectomy in patients who have diffuse osteoclastic breast cancer is extremely variable.

There is one special feature that I would like to emphasize which Dr. Pearson has already touched upon, that is, the question of the calcium and phosphorus metabolism. Hypercalcemia can be a very severe and, as in many of these patients, an extremely distressing part of diffuse osteoclastic metastatic disease. It interferes with the nutrition of the patient and with the patient's well-being; he refuses to eat and has severe constipation due to the loss of normal gastrointestinal motility; and in some of the patients whom we have studied, bilateral adrenalectomy has dramatically assisted in the management of the hypercalcemia.

(Slide) One patient had marked hypercalcemia resulting from a carcinoma of the breast with extensive osseous and soft tissue metastases. (Slide.) This is a study of the calcium and phosphorous metabolism; on the upper part of the slide are intake and urinary outputs; below is serum concentration of calcium in the red and phosphorus in the white. The patient had an oophorectomy. At a designated point, a bilateral adrenalectomy was also performed, which immediately led to an abrupt fall in the serum calcium level, a rise in the serum phosphorus level, and a return to a positive calcium balance.

Later the patient was on a rather standard and ordinary intake of calcium, and a positive balance was maintained for a long period of time without the recurrence of hypercalcemia. Almost immediately following the adrenalectomy she was relieved of obstipation, and had a marked increase in appetite and considerable relief of the bone pain.

The operation in this patient did not stop the progress of the disease, although it did make the patient a great deal more comfortable. She ultimately died of the cancer seven months after the adrenalectomy had been performed. The pathologic specimen taken from four different metastatic areas before adrenalectomy and subsequently at autopsy showed marked changes in the cellular appearance of the tumor which were ascribed to the absence of the adrenals.

Since our studies have been few, up to the present time the greatest value that has been derived from this procedure is obtaining the data that give us a somewhat better understanding of the various metabolic effects of the tumor and of the response of the patient to bilateral adrenalectomy. Actually, we have seen no patients in whom we feel that the progress of the disease has actually been interrupted, although Dr. Pearson demonstrated this in one patient.

DR. DANELY P. SLAUGHTER (Chicago, Ill.).—At the University of Illinois, we have been interested in this problem, too. To date, we have 25 patients who have been adrenalectomized. Seven of these were prostatic cancer patients, and we share Dr. Pearson and Dr. Randall's point of view that it is a fairly useless procedure, because we found little or no benefit. In eighteen breast cancer patients disseminated disease was far advanced, and these patients had ceased to respond to any other form of treatment. Sixteen of these we are able to report on, one died postoperatively, and one lived too short a time to be worth reporting. Of the 16, 7 showed definite objective improvement, with measurable regression, and 12 showed marked subjective improvement. Some of them also had objective change.

In the group with objective improvement, we had the same experience, that in 3 patients some areas of cancer regressed while new disease appeared simultaneously. The longest improvement, a very dramatic one, occurred in a young woman, 34 years of age, with very disseminated advanced disease, cervical nodes, local recurrence, and pulmonary and widespread bone metastases. The disease cleared up completely and the woman was clinically well. All evidence of disease disappeared except for recalcification evident on x-ray examination. That remission lasted 300 days, and then she rapidly developed recurrence which responded to no treatment; she is now dead.

In this study I think we learned one reason to explain why death is prolonged in some breast cancer patients. In our oophorectomy specimens, 40 per cent of the ovaries contained metastatic cancer and 50 per cent of the adrenal glands contained metastatic cancer bilaterally. I suspect that these patients castrate themselves and perform their own adrenalectomy because, in looking back, I think we have seen some breast cancer patients die with adrenal insufficiency.

PORTAL VENOGRAPHY VIA THE PORTAL AND PERCUTANEOUS SPLENIC ROUTES

Anatomic and Clinical Studies

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THE surgical management of portal hypertension is a subject which is currently the source of considerable interest, and not a little controversy, among surgeons both here and abroad. It is only a little more than a decade since A. O. Whipple[1] and one of us[2] focused attention on the importance of the portal venous bed and the role of portal venous obstruction. Thus was the term portal hypertension first introduced into the American literature. The evolution of portacaval shunts as a surgical method to combat the serious and usually fatal bleeding in these patients is also now well known, but not within our province to discuss at this time.[3-10]

In a paper[3] on portal hypertension read before this Society in 1940, one of us (L. M. R.) called attention to the paucity of accurate information on the normal anatomy of the portal venous system. At the same time, he discussed the anatomic variants with the meager information then available, and postulated on the importance of the site of portal-bed block in relation to these variants.

Of late, one of our group (G. A. D.) has relocated the comparatively unknown work of Walcker[11] on the anatomy of the portal system. This anatomist has given detailed descriptions of the normal anatomy of the portal bed together with the frequent anomalies of the secondary branches. Succeeding studies by Walcker[12] gave equally comprehensive details of the many acquired portacaval shunts (the "hepatofugale" circulation of Pick) that can develop in patients with cirrhosis and/or portal vein obstruction.

It is worthy of note that, with increased interest in surgical procedures about the head of the pancreas and portal system, our attenion has been focused anew on the anatomy of this area. Revealing and detailed anatomic studies of the vascular structures in this region have recently been reported. We refer particularly to the excellent articles by Falconer,[13] of Edinburgh, and Douglass[14] and Gilfillan[15] in this country.

Continuing studies on the problem of portal hypertension have focused our interest on the application of the technique of venography as a valuable adjunct in the diagnosis and surgical therapy of this syndrome. Due recognition is accorded the development of portal venography by Moore[16, 17] and Child[18-20] in this country and other workers abroad.[21, 22, 24, 25] A still later contribution has come from Europe, with the percutaneous injection of the spleen with

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opaque medium and the x-ray definition of splenic vein, portal vein, and collaterals if present.[23]

Our efforts have pursued two main directions: (1) roentgen examination of cadaver material in the "normal" subject and (2) operative portal venography in the human being, with special reference to its use in the selection of type of portacaval shunt.

Roentgen Definition of the Normal Anatomy of the Portal Venous Bed.—X-ray examinations were made on a series of fifty fresh post-mortem subjects. These normal anatomic studies were limited to material in which clinical and post-mortem findings clearly excluded the possibility of portal hypertension. We injected 200 to 250 c.c. of a thin barium sulfate mixture under minimal pressure into the superior mesenteric vein or inferior mesenteric vein. Using a 15 Ma. portable x-ray machine, x-ray pictures were taken. This roentgenographic method gave us a series of permanent records which we could study and restudy at leisure,[26] unlike the usual anatomic dissection which has to be laboriously and often incompletely recorded by hand drawings.

The portal complex, as we know, is formed by the confluence of the three major veins: the portal, splenic, and superior mesenteric. For clarity and brevity, we shall serially present a representative group of x-ray pictures (Figs. 1 through 4).

From these x-ray pictures we have found three major anatomic types involving the major trunk. These we have designated as the (1) tripod, (2) T, and (3) Y types. These types are determined by the angle formed by the portal and splenic veins (portasplenic angle). Reference to Fig. 5 will graphically depict the varying types found. The tripod type with an angle between 90 and 140 degrees was the prevailing form and was encountered in 80 per cent of our material; the T and Y types each occurred with about equal infrequency, that is, 10 per cent. This classification became apparent during our studies and is used by us as a generic descriptive device in the interpretation of the roentgenogram.

Configuration and Relationship of Major Veins in the Portal System.—The schematic pattern in Fig. 6 gives a summation of the proximal and distal terminations of all the major veins of the extrahepatic portal system. Fig. 6 also summarizes measurements of five of the major tributaries, both as to length and diameter. Our figures on the length of portal and splenic veins coincide very closely with the dissection studies of others.[14, 15] However, our diameter measurements differ considerably from Douglass'[14] figures in that the diameters of portal and splenic veins in our roentgenograms are appreciably greater than those in the source referred to. The Douglass figures were obtained by measuring collapsed veins after fixation for forty-eight hours. Our measurements were made from x-ray pictures of fresh unfixed cadaver material. Allowing for the 15 per cent magnification due to forty-inch target film distance, we believe our measurements more accurately approximate the in vivo situation, as the results given closely approximate the measurements we have made on the portal venogram of the living subject and our own direct measurements at the operating table.

We were able to confirm by roentgenogram the anatomic variants with respect to the point of entry of the major tributaries as they enter the portal system. Our experience as to the variations is in accord with the dissection findings of Falconer[13] and Douglass.[14] Reference is made to Fig. 7 for demonstration of the varying points of entry of two of the major veins, the inferior mesenteric vein and the coronary vein. Thus, the inferior mesenteric vein may join the splenic vein or the superior mesenteric vein, or enter in the crotch formed by the confluence of the splenic and superior mesenteric veins. The coronary vein also presents three varying points of entry, into the splenic or portal veins, or at the confluence of the two veins.

Technique of Operative Portal Venography.—Roentgen visualization of the portal venous bed at the time of operation is now routinely done in all our cases of portal hypertension. This involves the taking of two types of roentgenograms: (a) the splenic portagram and (b) the portal portagram. A brief definition of terminology is in order at this time. Portal venography has been defined by Moore and Bridenbaugh[16, 17] as "the contrast roentgen visualization of the portal vein and the intra-hepatic radicles." Since it was the intent of these authors to outline the extrahepatic and intrahepatic courses of the portal vein, the term is most explicit. With the extension of this technique by other workers[18-25, 27] and an ever wider visualization of the portal bed, it seems fitting to broaden the initial definition to include the entire portal venous system and any segment thereof. Thus, we shall speak of portal portagram and splenic portagram as subdivisions under the all-inclusive caption of portal venography.

(a) The splenic portagram depicts mainly the secondary and primary splenic trunks of the splenic vein, the portal vein, and the major collateral or collateral systems in the abdomen. Prior to surgical incision, the splenic portagram process is accomplished by the percutaneous injection of 40 to 50 c.c. of 70 per cent Urokon Sodium* into the splenic pulp through the ninth intercostal space. A 100 Ma. machine is used which permits exposure below one second. This is used in conjunction with a grid cassette. The film is taken when 30 to 40 c.c. of the solution has been injected. Laparotomy is then carried out through a short upper abdominal transverse incision. In preparation for (b) the portal portagram, the superior mesenteric vein is then isolated and cannulized with a Size 18 polyethylene catheter. Using a three-way stopcock and appropriate connecting tubing and manometer, venous pressure readings are first made. Then the medium is rapidly injected into the portal circuit within five to seven seconds. A preparation of 40 to 50 c.c. of a 30 per cent Urokon Sodium solution is injected and film exposure is made toward the end of the injection.

The Splenic Portagram and Portal Portagram as Aids in Selection of Type of Portacaval Shunts.—Our experience with this method has been limited to sixteen portal portagrams and five splenic portagrams. We now routinely take these two types of roentgenograms in most cases of portal hypertension. Using

*Solution supplied through courtesy of Mallinckrodt Chemical Works, St. Louis, Mo.

Fig. 1 (Case 4244).—Normal post-mortem portagram: tripod type, occurs in about 80 per cent of cases. Major tributaries follow a common pattern: inferior mesenteric vein enters splenic vein, coronary vein enters portal vein. *COR. V.* represents coronary vein; *G.E.P.V.*, gastroepiploic vein; *I.M.V.*, inferior mesenteric veni; *P.V.*, portal vein; *P.D.V.*, pancreaticoduodenal vein; *S.M.V.*, superior mesenteric vein.

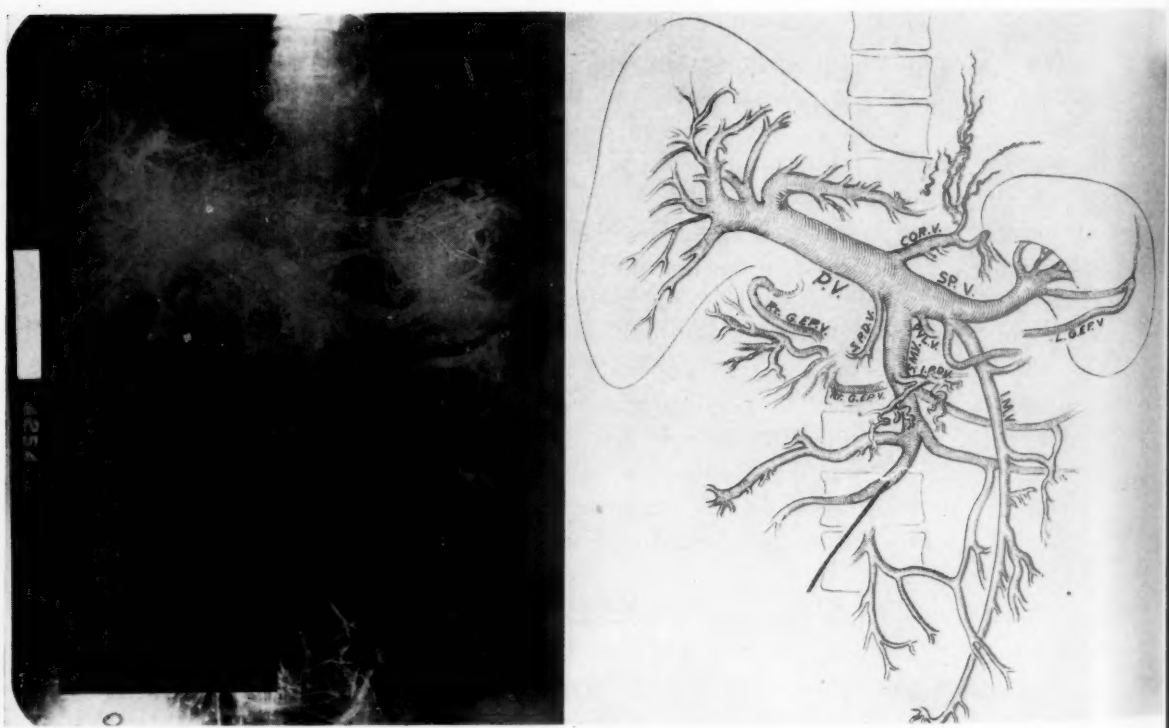


Fig. 2 (Case 4254).—Normal post-mortem portagram: T type, occurs in about 10 per cent of cases. Major tributaries follow a common pattern: inferior mesenteric vein enters splenic vein, coronary vein enters portal vein. (Note filling of normal fine branches in the region of lower end of esophagus.)

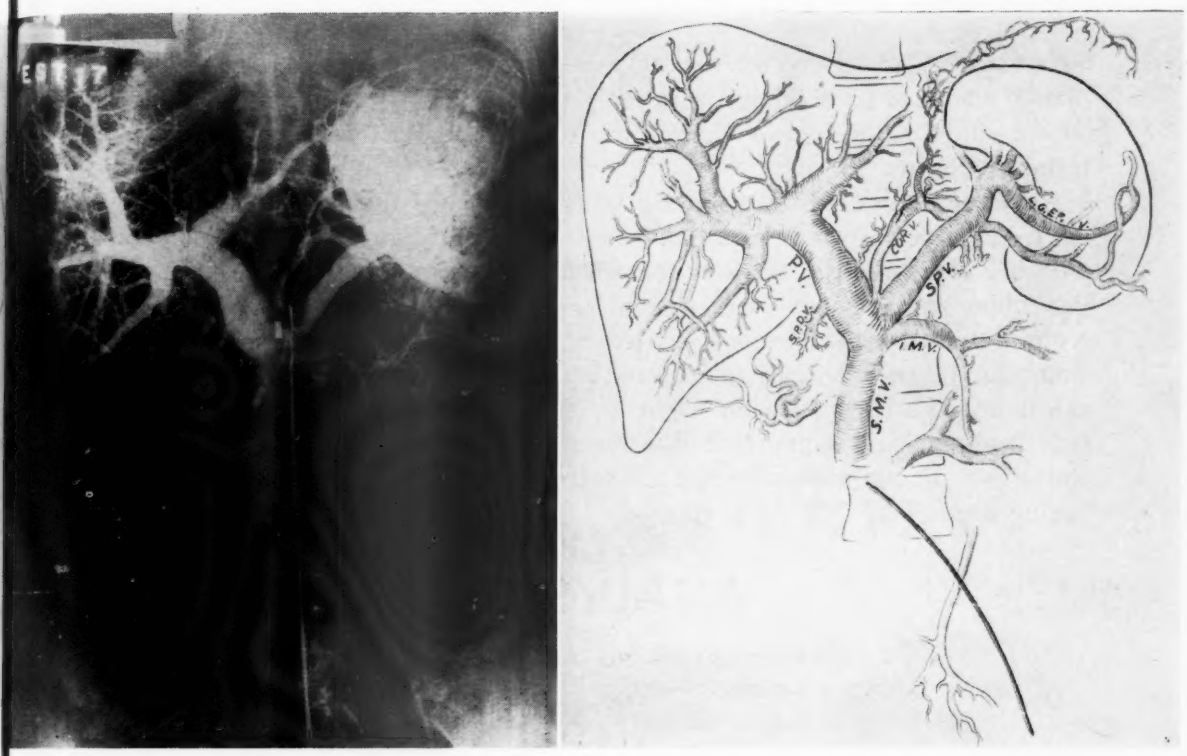


Fig. 3 (Case 4134).—Normal post-mortem portagram: Y type. Major tributaries present an unusual arrangement: coronary vein enters crotch formed by portal and splenic veins; inferior mesenteric vein enters crotch formed by superior mesenteric and splenic veins. Such a confluence formed by five veins, portal, splenic, coronary, inferior mesenteric, and superior mesenteric, is very rare.

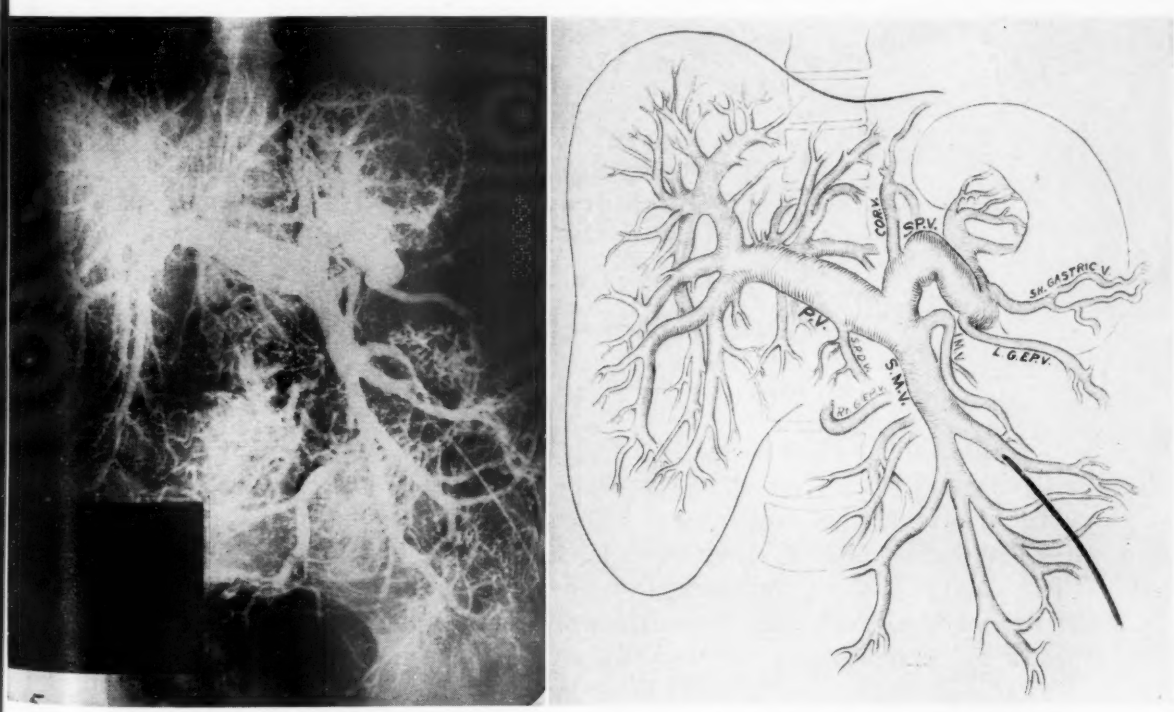


Fig. 4 (Case 5254).—Normal post-mortem portagram: tripod type. Major tributaries present fairly frequent combination: inferior mesenteric vein enters superior mesenteric vein, coronary vein enters splenic vein.

both methods, we believe, a more complete picture of the portal bed is procurable than is likely to be obtained using only one method. Furthermore, the use of both techniques minimizes the danger of nonvisualization in the event of a technical failure.

By the utilization of these two x-ray techniques at operation, we have derived valuable information on the anatomy and collaterals of the portal bed and, of more practical importance, we have had an accurate measurement of the caliber and patency of the portal and the splenic veins. This, along with certain clinical considerations, enables the surgeon to select the optimum type shunt for the specific patient in question. Thus, the upper transverse incision can be extended into either a right or left thoracoabdominal approach. Without roentgenologic support of this sort, surgeons electing to use a portacaval shunt in a patient with cirrhosis not infrequently find, only after a long, painstaking dissection, that the portal vein is not usable.

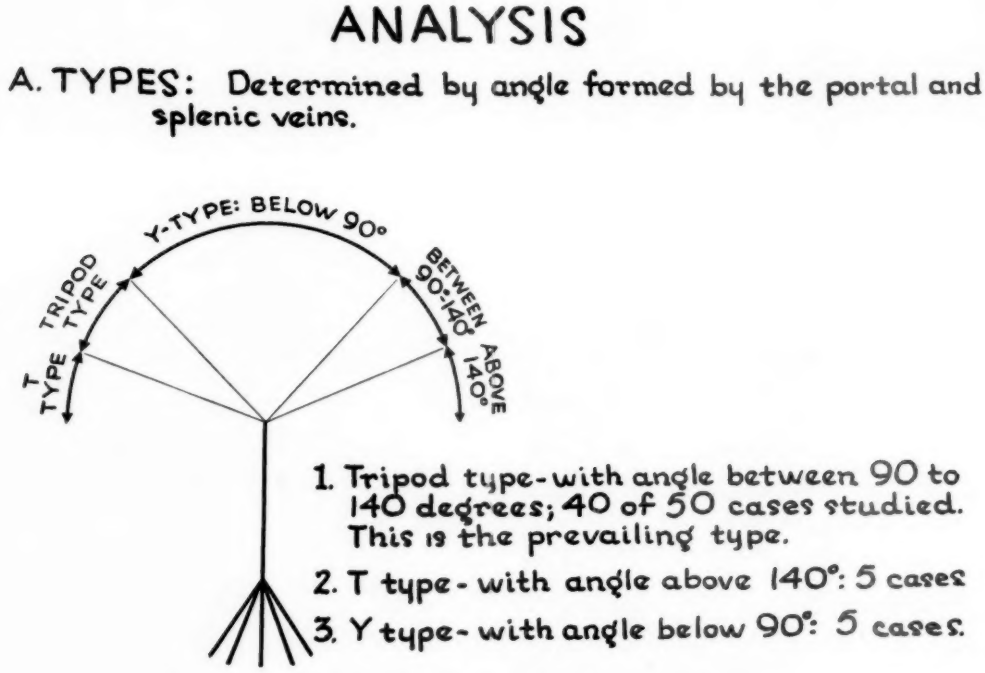

ANALYSIS
A. TYPES: Determined by angle formed by the portal and splenic veins.
Y-TYPE: BELOW 90°
TRIPOD TYPE
T TYPE
BETWEEN 90-140°
ABOVE 140°
1. Tripod type - with angle between 90 to 140 degrees; 40 of 50 cases studied. This is the prevailing type.
2. T type - with angle above 140°: 5 cases
3. Y type - with angle below 90°: 5 cases.

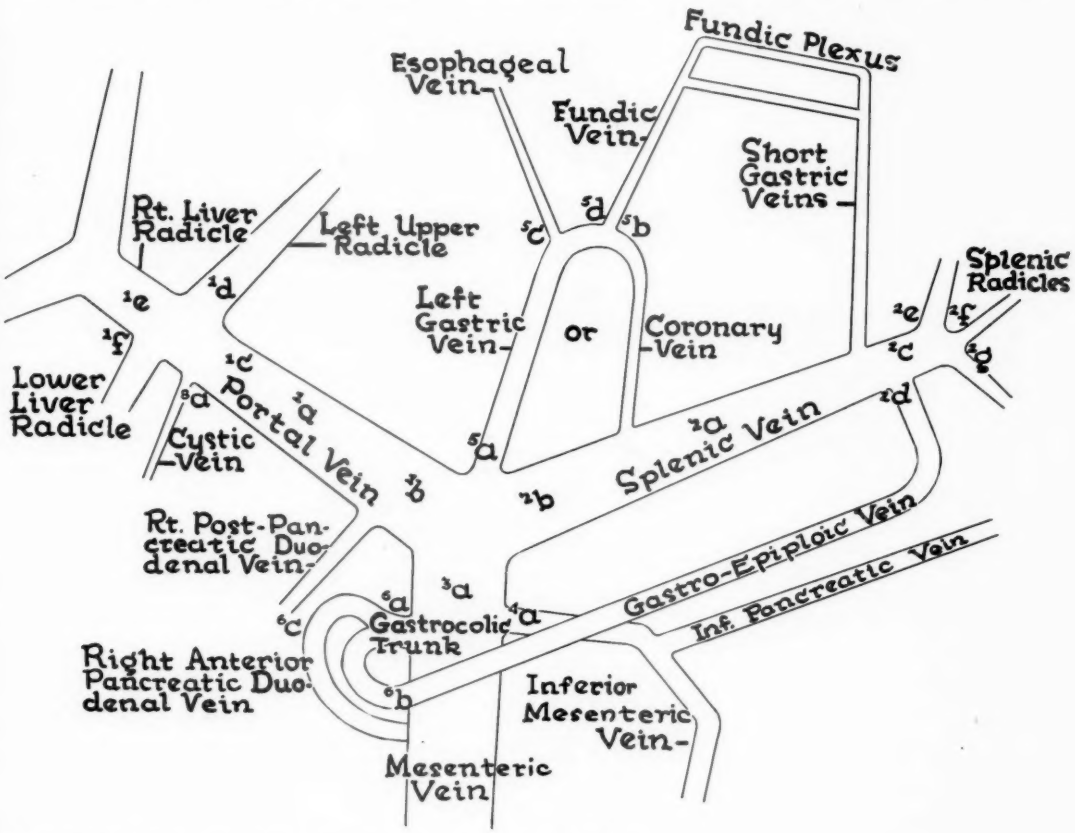
Fig. 5.—Graph depicting the three types of portal complex.

Obliteration of the portal vein by a bland thrombus can occur in patients with cirrhosis of the liver. The frequency of this lesion is not accurately known; suffice it to state that any surgeon with a broad experience in this field has, on occasion, been unable to carry out a portacaval shunt because of this complication. Cavernomatous transformation of the portal vein also leads to a similar hindrance to performance of a portacaval shunt and should conceivably be suspected by venography.

As a corollary, a splenorenal shunt may be impossible to perform or of dubious value in certain cases. In some patients with only moderate splenomegaly, the splenic vein may be of such small caliber as to preclude an efficient shunt,

using the splenorenal route. An anomalous bifid splenic vein may also result in vein structures so narrow or so occluded by thrombus, pancreatic cyst, etc., as to make vein anastomosis technically impossible. (In occlusion near the splenic hilum, only splenectomy is indicated.) Only by splenic portagram or portal portagram can the existence of such intravascular situations be accurately predicted early in the operation.

Generally, a very large spleen (with or without hypersplenism) usually connotes compensatory enlargement of the hilar vessels. This again, however,



Vascular measurements of the portal system

	Averages
1. Portal vein	
^{1}a. length	6.4 cm.
^{1}b. hepato distal diam.	23.0 mm.
^{1}c. hepato proximal diam.	19.0 mm.
^{1}d. lt. upper radicle diam.	15.0 mm.
^{1}e. rt. radicle diam.	18.0 mm.
2. Splenic vein	
^{2}a. length	9.0 cm.
^{2}b. hepato proxim. diam.	14.0 mm.
^{2}c. hepato distal diam.	10.0 mm.
3. Sup. mesenteric vein	
^{3}a. diameter	17.0 mm.
4. Inf. mesenteric vein	
^{4}a. hepato prox. diam.	6.0 mm.
^{4}b. hepato distal diam.	2.0 mm.
5. Left gastric vein	
^{5}a. hepato prox. diam.	5.0 mm.
^{5}b. coronary vein diam.	4.0 mm.
^{5}c. fundic vein diam.	3.0 mm.

Fig. 6.—Schematic pattern of the proximal and distal terminations of all the major veins of the extrahepatic portal system.

can be established by x-ray picture. The use of any vein in portacaval shunts (splenic or others) with a diameter of less than 1.0 cm. will, as a rule, result in insufficient lowering of portal pressure and, later, closure of the stoma.

Figs. 8 through 12, venograms taken at the operating table, are examples of the two types of portagrams described and illustrate some of the features already outlined. Accompanying legends give specific details in each instance.

DISCUSSION

The application of portal venography, in our opinion, offers a dynamic, accurate, and rational basis for the election of a specific type of veno-venous shunt in portal hypertension. Because of the information gleaned from these roentgenologic studies, the surgeon does not unwittingly commit himself to the use of the portal or splenic vein, only to find he has an inoperable situation.

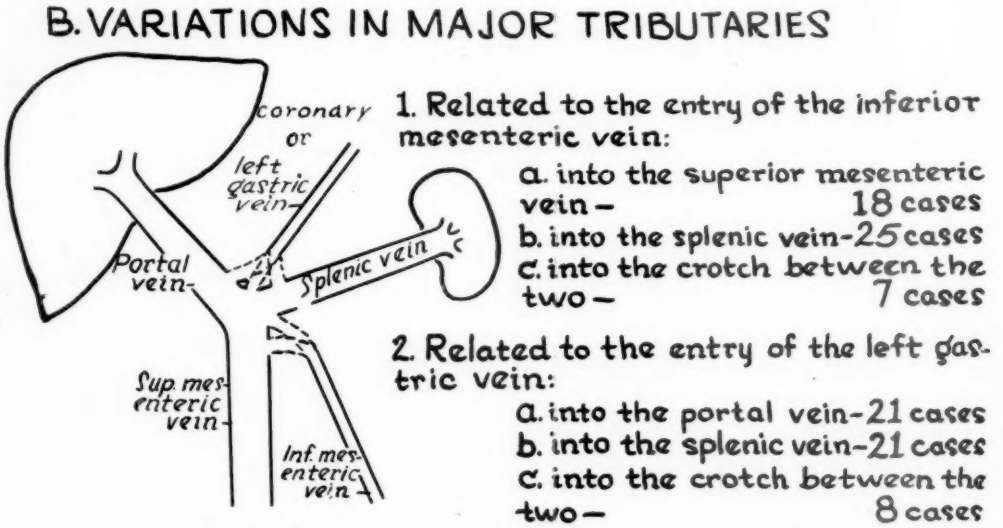

B. VARIATIONS IN MAJOR TRIBUTARIES
coronary or left gastric vein
Portal vein
Splenic vein
Sup. mes. enteric vein
Inf. mes. enteric vein
1. Related to the entry of the inferior mesenteric vein:
a. into the superior mesenteric vein – 18 cases
b. into the splenic vein – 25 cases
c. into the crotch between the two – 7 cases
2. Related to the entry of the left gastric vein:
a. into the portal vein – 21 cases
b. into the splenic vein – 21 cases
c. into the crotch between the two – 8 cases

Fig. 7.—Graph depicting the varying points of entry of two of the major veins, the inferior mesenteric vein and the coronary vein.

The use of both types of roentgenograms in most cases gives a much more accurate picture of the portal venous bed than would either technique singly. As graphically shown in the portagrams reproduced here, nonfilling of vessels in the splenic portagram is supplemented by filling of the same vessels in the portal portagram and conversely.

The previously cited cases and accompanying venograms are only a few examples of other similar, confirmative studies. A terse digest of these data may be expressed as follows, with an indication as to when the surgeon may elect to perform a portacaval or a splenorenal shunt:

1. Portal hypertension with moderate splenomegaly, small caliber splenic vein, large patient portal vein: portacaval shunt.

2. Portal hypertension with marked splenomegaly, large caliber splenic vein, plus hypersplenism: splenectomy and splenorenal shunt.

3. Portal hypertension, obliterated portal vein (bland thrombus or cavernomatous transformation): splenectomy and splenorenal shunt.

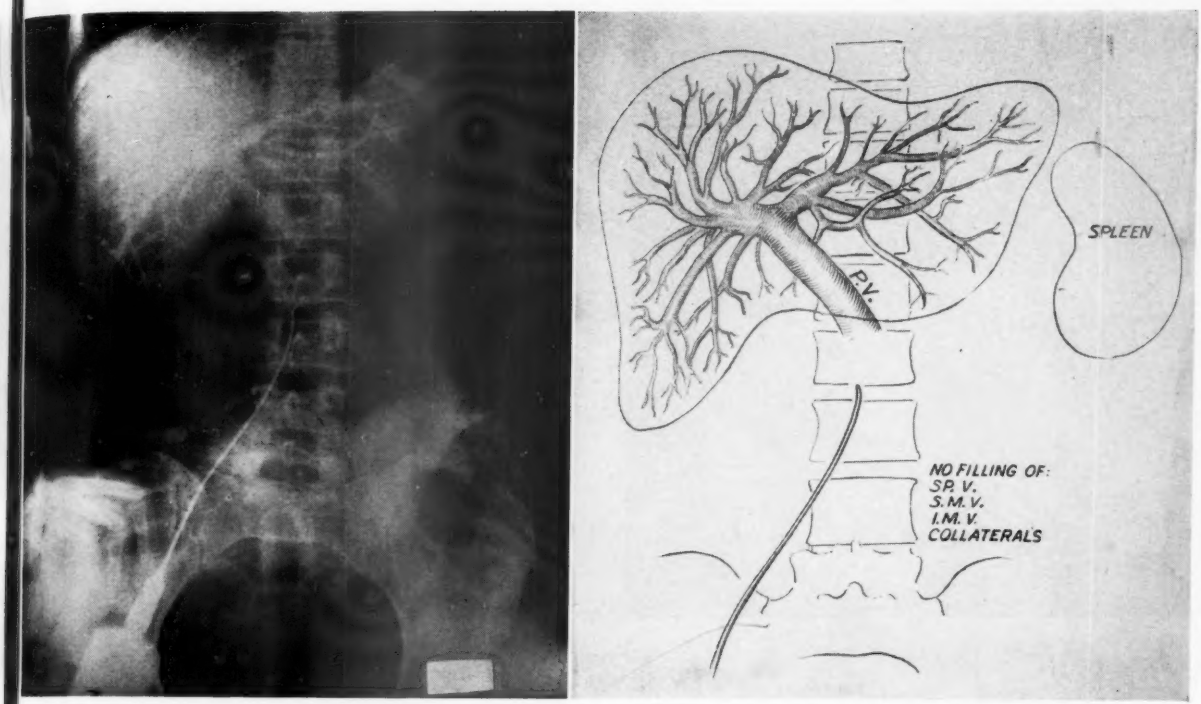


Fig. 8 (Case 45675).—Normal portal portagram. Branch of superior mesenteric vein cannulized at surgery. Blood flow is hepatopetal and rapid. Therefore, only the portal vein and its intrahepatic branches are ordinarily visualized in the normal portagram. Compare with cases of portal hypertension in Figs. 9 through 12. In doubtful cases portal venography may prove useful in confirming or excluding a diagnosis of portal hypertension.

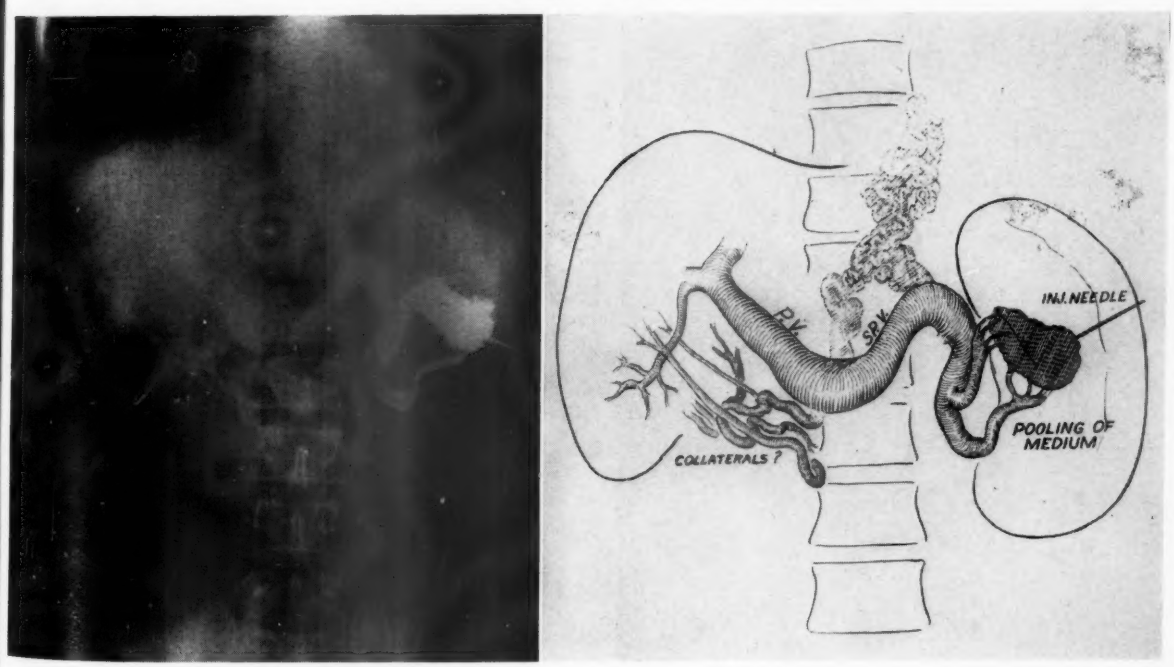


Fig. 9 (Case 43412).—Portal hypertension in cirrhosis of liver with hypersplenism. Splenic portagram: tripod type. Dye flow is hepatofugal. (Note unusual tapering of portal vein as it approaches liver.) Collateralization is mainly over coronary vein. (Note varices in region of lower esophagus and cardia of stomach.) Collateral veins are also seen on the right side inferior to the portal vein. These may extend upward to anastomose with the liver veins directly or may possibly communicate retroperitoneally with the inferior vena cava. Splenic vein is well delineated. Because of large diameter, splenic vein was usable for splenorenal shunt which was performed following splenectomy.

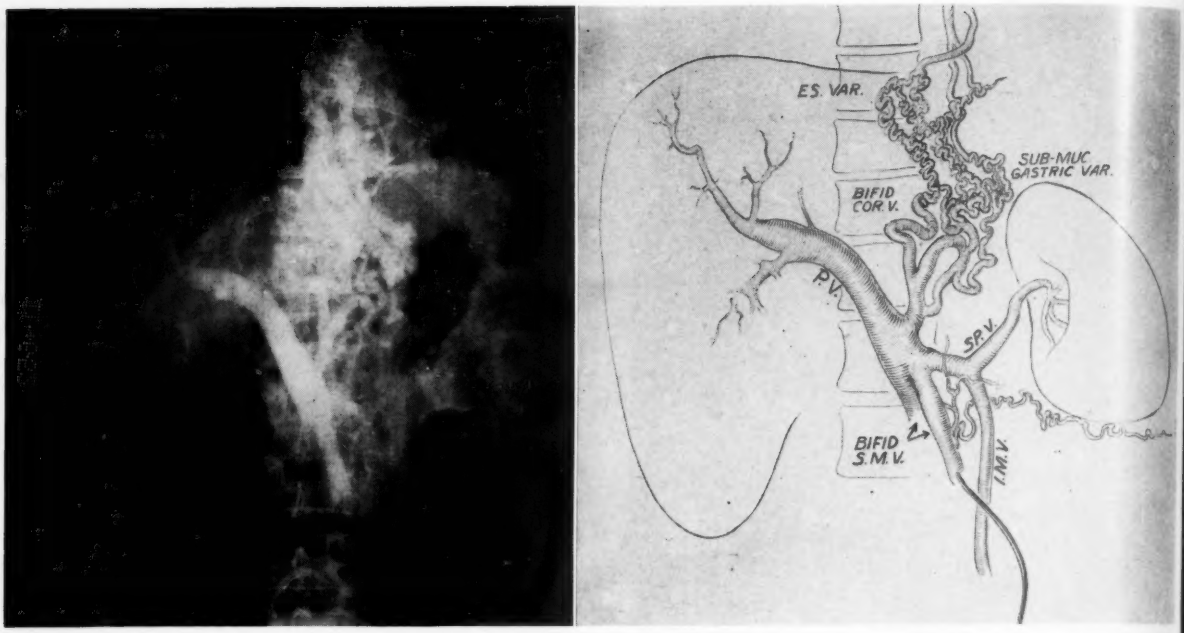


Fig. 10 (Case 42036).—Portal hypertension in cirrhosis of liver. Portal portagram: Y type. Superior mesenteric vein cannulized at surgery. This followed a splenic portagram. (Note diffuse density representing residual dye in splenic area.) Dye flow in portal system is hepatofugal over two chief collaterals, the coronary and the inferior mesenteric veins. (Note submucosal gastric varices in the cardiac region of the stomach and esophageal varices in distal esophagus.) Hemiazygos vein is also visualized. Because splenic vein is below 1.0 cm. in diameter and portal vein is large, portacaval shunt was used rather than splenorenal shunt.

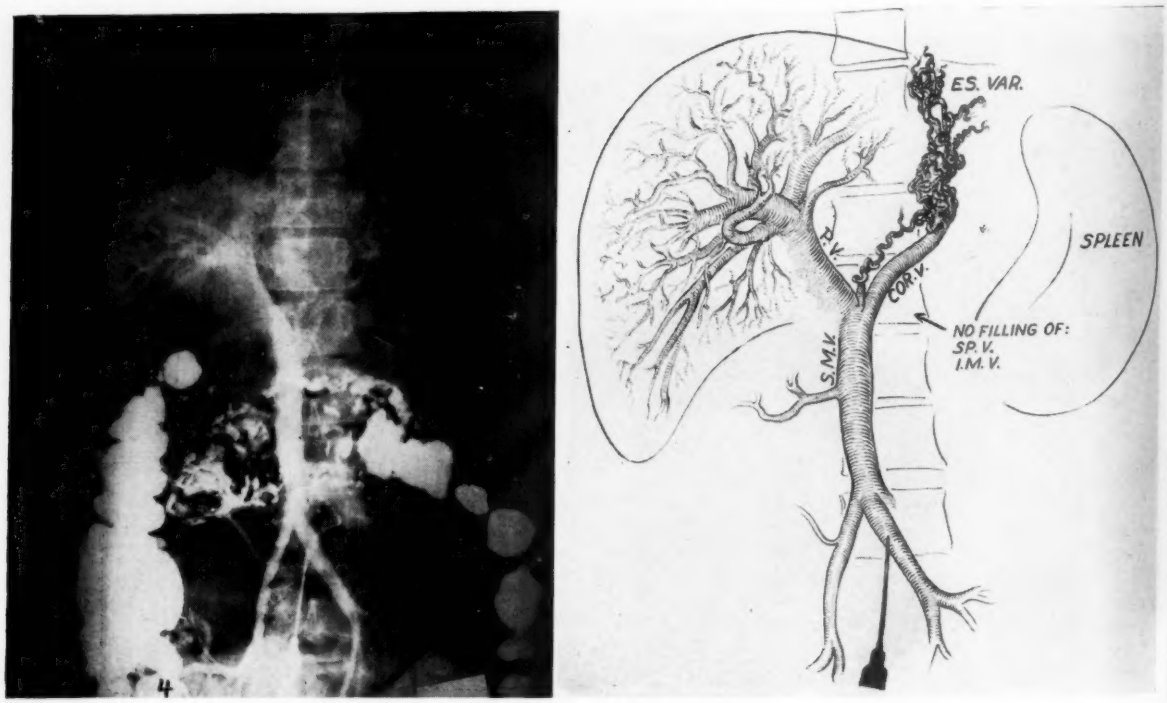
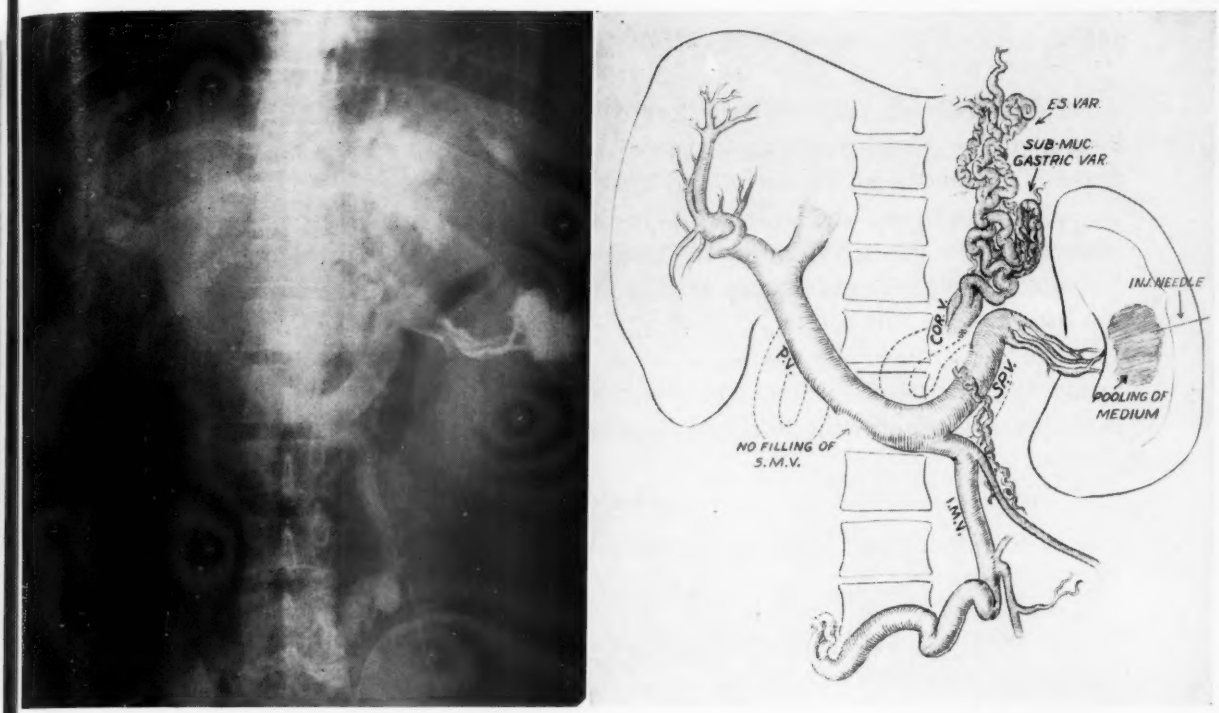
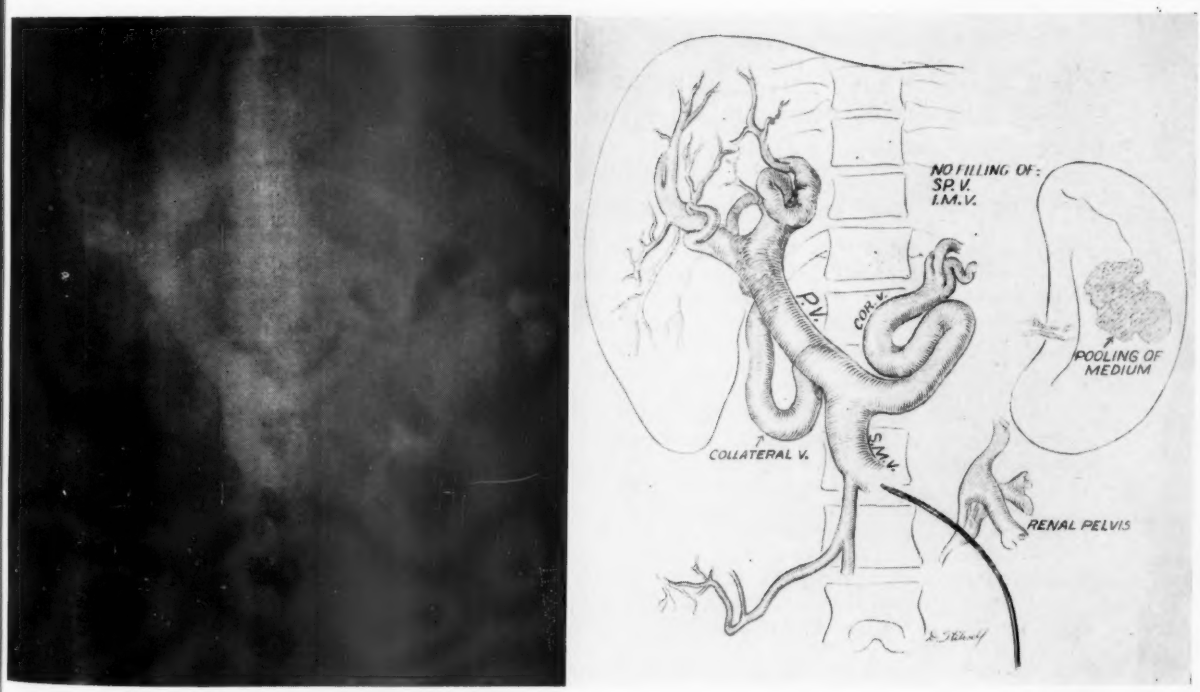


Fig. 11 (Case 40241).—Portal hypertension of undetermined etiology. Portal portagram, type not determinable because of failure of filling of splenic vein. Collateralization is chiefly via the coronary vein. (Note esophageal varices.) Collateral circulation with the inferior vena caval system is probably effected via branches of the superior mesenteric vein in the right lower quadrant. Filling of the branches of the superior mesenteric vein is ordinarily not expected unless blood flow in this direction exists on a collateral basis. This patient had hypersplenism and a very large spleen. Since the latter is usually indicative of a splenic vein of large diameter, splenectomy was followed by a splenorenal shunt. A splenic portagram would have been useful in delineating the splenic vein, giving immediate information as to size and position. (Case antedated our use of splenic portagraphy.)



A.



B.

Fig. 12 (Case 40514).—*A*, Portal hypertension in cirrhosis of liver. Splenic portagram: Y type. Dye flow follows blood flow in hepatofugal direction. Collateralization is achieved chiefly over coronary and inferior mesenteric vein systems. (Note large submucous gastric varices as well as esophageal varices.) Intrahepatic portal branches are sparse. Dotted lines outline faintly visualized, dilated and tortuous coronary vein on the left side and either coronary or, possibly, anomalous collateral with liver or pancreaticoduodenal vein on the right side. Splenic portagram assures visualization of splenic vein.

B, Portal portagram. (Complements splenic portagram shown in *A*.) Superior mesenteric vein branch cannulized at surgery. Splenic vein is not visualized but portal vein is more clearly defined than in *A*. This study, furthermore, permits more ready identification of dilated collaterals only faintly visualized in splenic portagram. (See dotted lines in *A*.) Since both portal and splenic veins in this case are equally usuable for anastomosis, operator's choice is not limited. He may carry out either a splenorenal shunt or a portacaval shunt.

Admittedly, in the surgical therapy of portal hypertension, the use of the largest caliber vessel available will most efficiently and permanently maintain a patent shunt between the portal and systemic veins.

Although portal venography has been initiated and pursued with increasing interest by several investigators in American clinics, the adoption of the splenic portagram and its combined use with the portal portagram is herein reported for the first time in this country.

Further clinical experience will, no doubt, extend the usefulness of portal venography in the surgical treatment, not only of portal hypertension, but probably also of other lesions in and about the pancreas, liver, and upper abdomen.

SUMMARY

1. Roentgenograms of the portal venous bed after injection with radiopaque medium have been valuable in studying the normal anatomy of this system.

2. Three major anatomic types have been found with respect to the relative position of splenic to portal vein; these have been designated as the tripod type, T type, and Y type.

3. The principal secondary tributaries entering the portal bed are subject to considerable variation as to point of entry. These variations have been discussed.

4. Operative portal venography using sequentially the two techniques of splenic portagram and portal portagram has proved to be a valuable aid in the rational selection of portacaval or splenorenal shunt in the cases described.

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DISCUSSION

DR. ELLIOTT HURWITT (New York, N. Y.).—I would like to congratulate Dr. Rousselot on his beautiful presentation, and add just one word of caution with regard to its application. At the Surgical Section of the New York Academy of Medicine last week, we presented three cases of massive hematemesis due to splenic vein obstruction secondary to lesions in the tail of the pancreas. At exploration, the hematemesis in two of these cases was secondary to carcinoma of the tail of the pancreas, and in the third it was due to involvement by Hodgkin's disease. If Dr. Rousselot's technique had been applied, with a preliminary subcutaneous splenogram, the splenic vein would have been found to have been obstructed in all three of these cases.

At the subsequent laparotomy, through the short transverse upper abdominal incision, the diagnosis would have been obvious in the case of Hodgkin's disease and in one of the cases of carcinoma. Thorough exploration had been carried out on the third patient, however, a few weeks previously at another hospital, and had been sent to us for a shunt because of the huge intra-abdominal veins and the large spleen. In the course of mobilizing the spleen, we encountered a small carcinoma in the tail of the pancreas, totally unsuspected and completely obstructing the splenic vein. I believe that this might not have been demonstrated by the incision that Dr. Rousselot recommends. This is all the more important, because it is possible that the procedure used for the third patient may represent a cure for carcinoma of the pancreas. When the frozen section of the mass in the tail of the pancreas was reported positive for carcinoma, the remainder of the body of the pancreas was removed; there was no evidence of malignancy in the second specimen submitted. All three of these patients were relieved of the massive hematemesis by this procedure. It is possible that we might have been misled in this third case, if we had allowed the technique proposed by Dr. Rousselot to have made the differential diagnosis for us and had proceeded with a porta-caval shunt.

DR. ROUSSELOT (Closing).—I cannot entirely agree with Dr. Hurwitt on this matter. I feel that the upper transverse abdominal incision made preparatory to exploration and portal venography lends itself surprisingly well to resection of the tail or body of the pancreas in the event that such a procedure is indicated. Such was our intent in planning this type of incision, as mentioned in the text of our paper. If necessary the incision can be carried into the right or left chest, again depending on the indication.

EXPERIENCES WITH PORTACAVAL ANASTOMOSIS IN THE TREATMENT OF PORTAL HYPERTENSION

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IN THE past few years the portacaval venous shunt has become a standard procedure in the treatment of portal hypertension. Since this operation was revived by Whipple[1] and Blakemore,[2] many surgeons have contributed to its technical improvement, and the mortality rate has been reduced to an acceptable level. Encouraging results have been reported by Blakemore[3] and others[4-6] in dealing with the serious problems of bleeding esophageal varices and wasting ascites, the most disabling complications of portal hypertension. Most authors have stressed the fact that the shunt operations do not affect the underlying pathology but merely provide a mechanical relief for hypertension within the portal system. There is no doubt that a successful shunt may deviate sufficient portal blood to produce a temporary drop in pressure and that, coincident with this drop, the manifestations of portal hypertension may be relieved. However, natural anastomoses occur between the portal and caval systems in cases of portal hypertension and, although many of these are larger than the average portacaval shunt, they do not effectively relieve the pressure. Beswick and Butler[7] and Learmonth[8] have reported cases in which fatal bleeding occurred from esophageal varices, yet at autopsy large natural portacaval anastomoses were found.

There are many factors besides increased portal pressure which are involved in the production of esophageal varices, and massive hemorrhage may occur even in the absence of portal hypertension. Rack, Mincks, and Simeone[9] have recently reviewed the literature and reported such a case.

Tocantins[10] has classified these factors into three groups (Fig. 1).

1. *Extravascular defects:* The mucosa of the lower esophagus is raised in longitudinal ridges and the veins lie in the submucosa directly beneath the epithelium. They are thus subject to mechanical trauma from swallowed food and diaphragmatic movement. In addition, regurgitation of acid gastric juice plays an important role in the production of mucosal ulcerations.

2. *Vascular defects:* Due to the mechanical factors of diaphragmatic movement, negative intrathoracic pressure, and portal hypertension the vein wall becomes atrophied and this predisposes to rupture.

3. *Intravascular defects:* Deficiencies in the clotting mechanism exist in many cases of portal hypertension. Chronic congestion of the spleen leads to increased destruction of platelets, and impaired liver function causes hypoprothrombinemia.

Read at the meeting of the Society of University Surgeons, St. Louis, Mo., Feb. 12-14, 1953.

It is obvious that relief of portal hypertension will correct only one of these factors and there is reason to doubt whether such a measure will be of great value in the long-range therapy of the disease. Furthermore, in patients with cirrhosis a portacaval shunt may adversely influence the underlying liver disease. It is true that the cirrhotic liver can tolerate an Eck fistula, but it is difficult to see how such a procedure can have any beneficial effect and evidence is accumulating to show that the reverse is true.

An Eck fistula reduces the liver blood flow in the dog and this leads to interference with several hepatic functions. Whipple[11] has described impaired protein synthesis in such animals, and Hallett and his co-workers[12] have noted a fall in hepatic oxygen consumption. Mann[13] pointed out many years ago that hepatic insufficiency occurs more rapidly if the circulation to the liver is impaired.

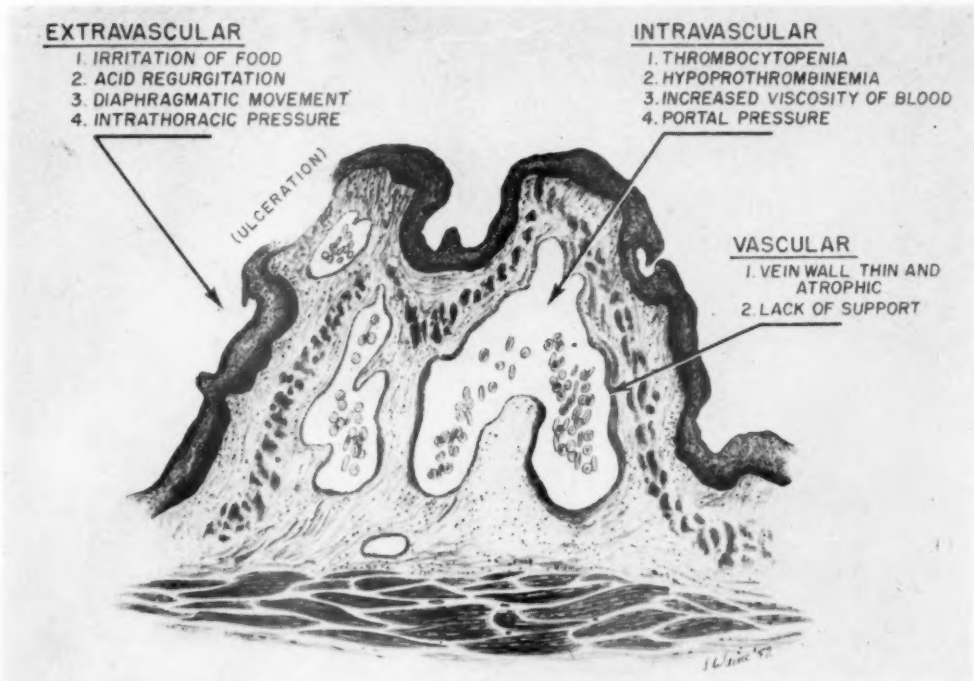
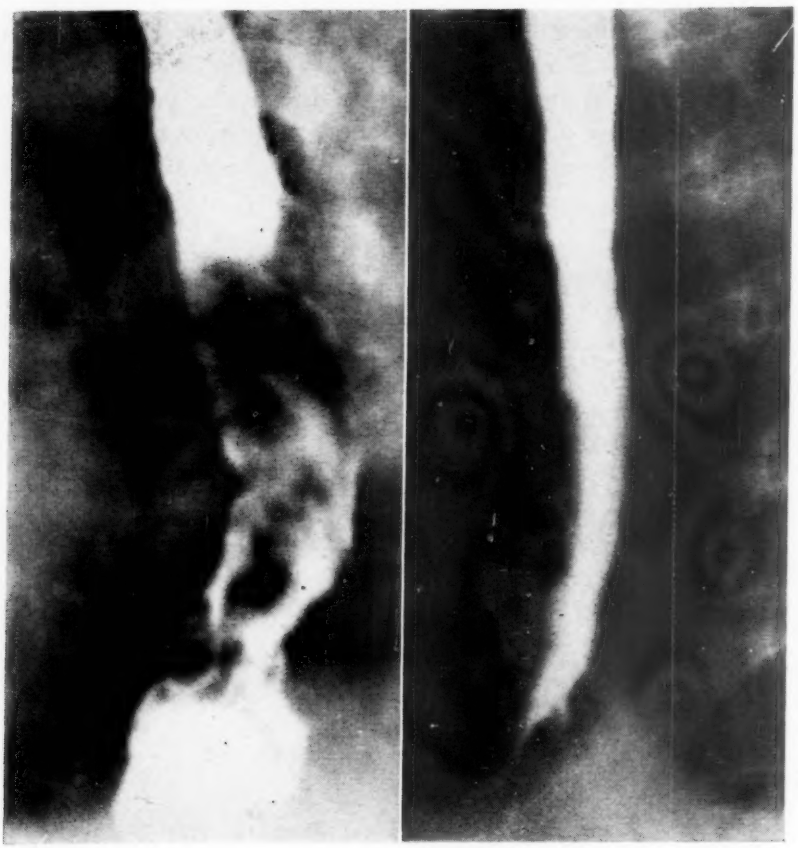


Fig. 1.—Diagram showing factors influencing bleeding from esophageal varices.

Bradley and associates[14] have recently demonstrated that in the human being with cirrhosis a portacaval shunt produces a definite decrease in hepatic blood flow. The exact significance of these observations is still uncertain and it is impossible to predict the effect of a shunt operation in terms of life expectancy in the patient with cirrhosis. However, since so many controversial points arise on a theoretical basis, it is essential to analyze clinical experiences with this operation in order to determine its proper place in the treatment of portal hypertension.

Clinical Material.—In the past five years, 30 patients have been subjected to surgery for the relief of portal hypertension. In 20 patients the cause was

cirrhosis of the liver, in 8 it was extrahepatic obstruction of the portal system, and in 2 the obstruction was due to a vascular anomaly of the portal veins within the liver. In all patients esophageal varices were present and gastrointestinal bleeding was the chief complaint. In the group with cirrhosis, ascites was evident in 6 patients.



A. *B.*

Fig. 2 (Case 1).—Esophageal studies showing large varices preoperatively (*A*), which have regressed three months after splenorenal anastomosis (*B*).

In 5 patients (16 per cent of the total series) the operation was abandoned because of the technical difficulties imposed by large collateral veins or because of the poor condition of the patient. Since all of these procedures were carried out by the same surgeon it is felt that this represents an average experience with this type of operation. In one case splenectomy alone was considered sufficient, and in twenty-four cases a shunt operation was carried out. Of these, fourteen were splenorenal anastomoses and ten were portacaval of the side-to-side type. There were two operative deaths, a mortality of 6.6 per cent. One fatality was due to hepatic failure in a patient with cirrhosis and the second was due to hemorrhage from peptic ulceration of the esophagus. Both deaths occurred in patients in whom a shunt operation had been abandoned.

Results of Operation.—Twenty-five patients with completed operations survived the procedure and are available for follow-up. In this group, 1 patient had splenectomy alone for Banti's syndrome and 24 had a shunt operation, 17 for cirrhosis and 7 for extrahepatic portal obstruction. The follow-up period ranges from one to five years.

Cirrhosis of the Liver.—The results of operation have been rather disappointing in this group. Liver function tests have shown no improvement in any patient but have tended toward increased liver damage in all.

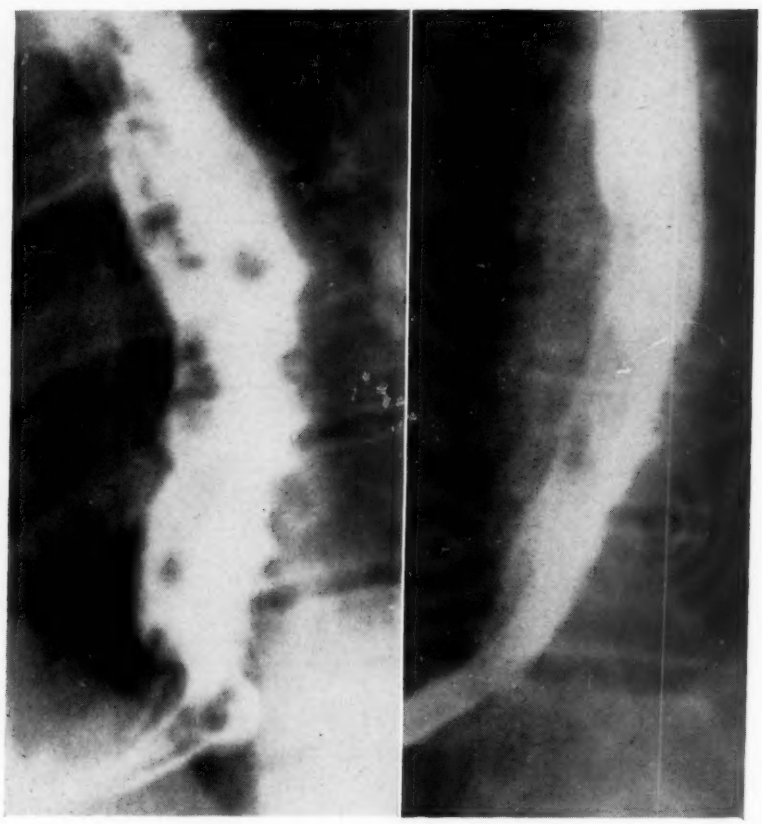
Fig. 3 (Case 1).—Autopsy specimen ten months after operation. The liver is extensively diseased and only small islets of hepatic tissue remain.

Four patients went into acute hepatic failure after surgery and were comatose for periods of from twenty-four to forty-eight hours. All of these patients recovered, but all died within one year of liver failure despite the fact that esophageal varices and ascites had disappeared. This may be a process similar to that reported by Rappaport, Borowz, and Lotto.[15] These workers found that, in dogs in which liver circulation had been impaired by hepatic artery ligation, portacaval anastomosis produced ischemic liver necrosis, coma, and death. The following case report illustrates a typical example.

Case 1.—C. S., a 59-year-old man, was admitted to the Royal Victoria Hospital, Montreal, in November, 1948, with a diagnosis of cirrhosis of the liver of two years' duration. Chief complaints were ascites and recurrent gastrointestinal hemorrhages. Investigation revealed large esophageal varices and impaired liver function with Bromsulphalein retention of 35 per cent and a reversed albumin-globulin ratio. He improved somewhat on dietary therapy and on Dec. 6, 1948, splenorenal anastomosis was performed. The initial portal pressure was 300 mm. of saline solution and this was reduced to 180 mm. of saline solution. Postoperatively

the patient became comatose and jaundiced, but after forty-eight hours he improved and made a gradual recovery. He was tapped several times in the first month after operation, but the ascites then disappeared completely and he was able to return to work. The esophageal varices regressed and there were no further episodes of bleeding (Fig. 2). Ten months after operation he became jaundiced and comatose and expired within a few days. At autopsy the shunt was patent and there were no esophageal varices, but the liver showed advanced cirrhosis with only small islands of functioning hepatic tissue (Fig. 3).

At the present time, 9 patients in this group have derived temporary benefit from operation but have relapsed or died within a period of one year. Five patients have shown no improvement, and 3 have remained well for more than one year. A typical example is Case 2.



A. *B.*

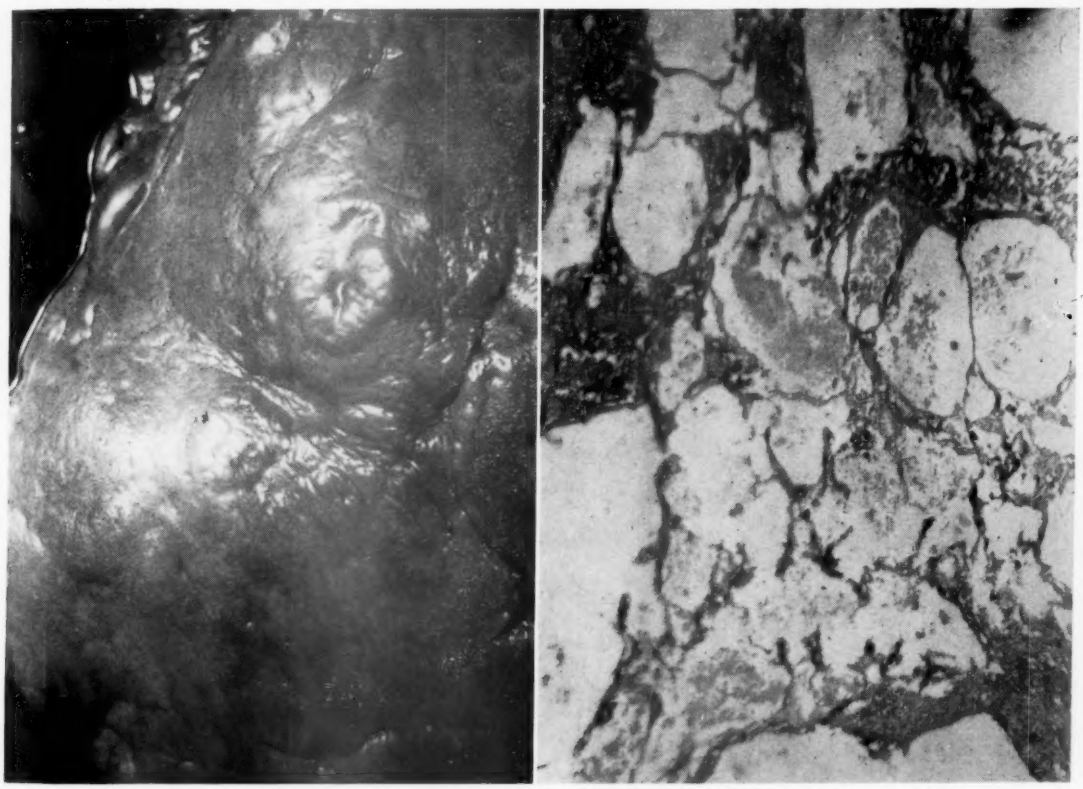
Fig. 4 (Case 2).—Barium swallow showing large varices preoperatively (*A*), which have decreased in size two months after a portacaval shunt (*B*).

CASE 2.—L. V., a 40-year-old man, was admitted to the Royal Victoria Hospital, Montreal, in February, 1948, complaining of repeated episodes of gastrointestinal bleeding. He had the first hematemesis in 1940, and in 1947 laparotomy had established the diagnosis of cirrhosis of the liver. Barium swallow revealed large esophageal varices. The liver function tests showed moderate impairment with a Bromsulphalein retention of 26 per cent, a cephalin flocculation of 3+, and a thymol turbidity of 7.0.

Splenorenal anastomosis was carried out on March 23, 1948, and the patient made an uneventful recovery. The esophageal varices regressed (Fig. 4) and despite the fact that

liver function tests showed increased impairment the patient remained well with no recurrences of bleeding for a period of four years. In February, 1952, he was readmitted to the hospital with recurrent bleeding, and he expired. No autopsy was obtained, but esophageal varices were visualized by roentgenogram.

This case represents a relatively good result but, unfortunately, such a lasting remission has been attained in only 18 per cent of the patients with cirrhosis. It is true that 12 patients (70 per cent) of this group have received initial benefit from the operation but in 9 the improvement has been transient. All of the deaths or relapses have been accompanied by liver failure and it has been our impression that these patients are more susceptible to exacerbations of hepatic damage. A great deal of further study will be necessary to clarify this point.



A. *B.*

Fig. 5.—Liver of patient with hereditary hemorrhagic telangiectasia showing intrahepatic vascular anomalies which produced portal obstruction. *A*, Gross view; *B*, microscopic view.

Extrahepatic Portal Obstruction.—In these cases, liver function has been normal and there has been no evidence of cirrhosis on liver biopsy. Theoretically this group should respond well to shunt operations and, in this small series, the results have been superior to those obtained in patients with cirrhosis.

All patients have received temporary benefit from surgery with regression of esophageal varices and cessation of bleeding. Since all patients have had evidences of hypersplenism it is difficult to attribute this improvement to the shunt alone. In three cases the improvement has been lasting and these patients

are still well three, two and one-half, and two years after operation. Four patients have had a temporary remission of symptoms and have then had recurrent bleeding. In 2 of these persons exploration revealed an extensive thrombosis, not only of the anastomosis, but also of the entire extrahepatic portal venous tree. These findings suggest that the factor which initiates the original portal thrombosis may continue to be active and cause gradual progression of the disease. The single patient with splenic vein thrombosis treated by splenectomy was well for sixteen months and then developed recurrent bleeding. At exploration, extensive thrombosis of the portal venous system was found and there were cirrhotic changes in the liver. An esophagogastrectomy was performed but this patient continues to have episodes of hemorrhage from esophageal varices.

Fig. 6.—Barium swallow showing esophageal varices.

Two cases of portal obstruction due to intrahepatic vascular anomalies have been observed (Fig. 5) and they present many features of interest. Both patients, a father and son, suffered from hereditary hemorrhagic telangiectasia and both had recurrent episodes of gastrointestinal hemorrhage from esophageal varices (Fig. 6). At operation on the father, a portal pressure of 400 mm. of saline solution was recorded and telangiectases were seen in the liver. A biopsy confirmed the diagnosis of an intrahepatic vascular anomaly producing portal obstruction. Operation was abandoned because of acute cardiac failure and the patient subsequently died from a massive gastrointestinal hemorrhage.

Autopsy showed that acute peptic ulceration of the esophagus was the cause of the final bleeding episode (Fig. 7).

The son was subsequently explored and an identical hepatic anomaly was discovered. The portal pressure was 380 mm. of saline solution. A side-to-side portacaval anastomosis was performed and the portal pressure reduced to 200 millimeters. Several months later the patient had recurrent bleeding and exploration was carried out again. The anastomosis was functioning and the portal pressure was 150 mm. of saline solution. Because of the finding of a high gastric acidity, a 90 per cent gastric resection was carried out, the spleen was removed, and a bilateral vagectomy was performed. The patient made an uneventful recovery and has had no episodes of bleeding for the past two years.

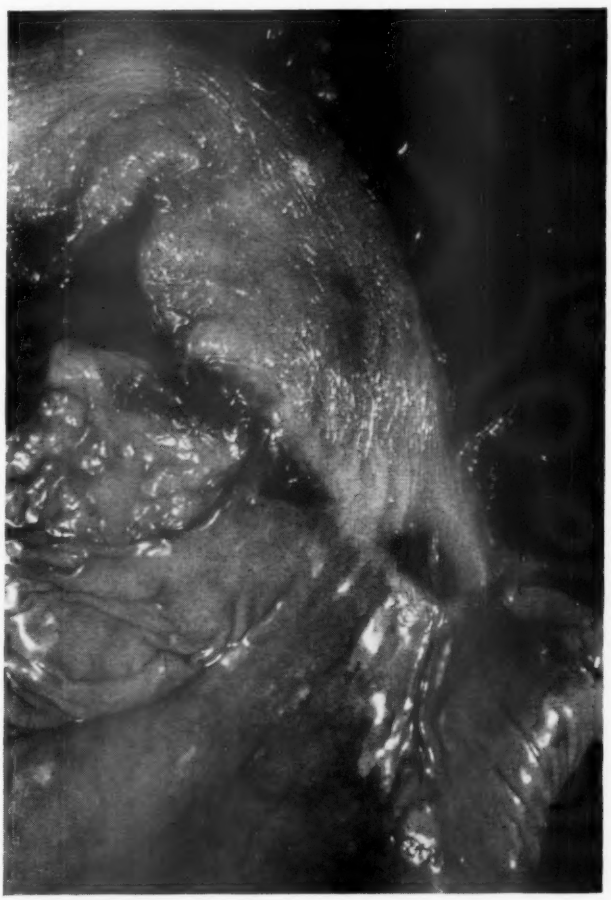


Fig. 7.—Autopsy specimen from patient with portal obstruction due to intrahepatic vascular anomalies. The final episode of bleeding was from peptic ulceration of the esophagus.

DISCUSSION

From this limited experience it appears that the portacaval shunt has several defects in the treatment of portal hypertension. It corrects only one of the factors responsible for bleeding from esophageal varices and it does reduce the blood supply to the liver.

The majority of patients in this series have received immediate benefit in the regression of esophageal varices and the cessation of gastrointestinal bleeding. This improvement has been temporary in most cases and nearly all of the patients with cirrhosis have shown evidence of increasing hepatic damage within one year or less. Three of 17 patients in this group have remained well for more than two years.

In patients with extrahepatic portal obstruction the results have been slightly better; all have benefited immediately and in 3 of 7 the benefit has been lasting.

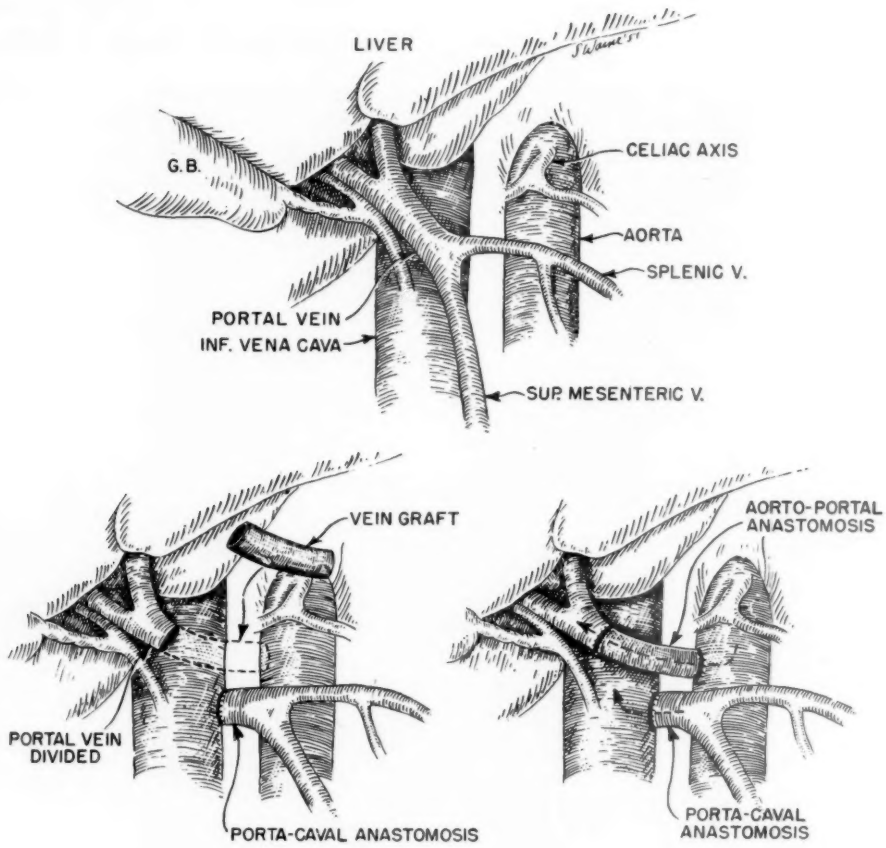


Fig. 8.—Diagram showing process of arterialization of the portal vein.

The chief concern in patients with cirrhosis has been that of depriving the liver of a portion of its blood supply, and an attempt has been made to obviate this by grafting a systemic artery into the proximal stump of the portal vein (Fig. 8). An experimental animal can live with an arterialized portal vein as the sole source of liver circulation and show no impairment of liver function. (This work is being reported elsewhere in detail.) Unfortunately, no successful operation of this nature has been carried out in the human being.

In the patients who did not have cirrhosis, the operation of splenectomy, high subtotal gastric resection with vagotomy, and periesophageal vein ligation

has been carried out in 2 patients with immediate excellent results. It appears likely that relief of hypertension alone will not be adequate in all cases of bleeding esophageal varices and it would seem rational to correct, in addition, the factors of acid regurgitation and hypersplenism. No single operation is ideal in this condition and it is only by analysis of long-term results that we can properly evaluate the many procedures advocated.

SUMMARY AND CONCLUSIONS

1. The rationale of portacaval anastomosis in the treatment of portal hypertension has been reviewed.

2. The results of surgery in thirty cases (twenty of cirrhosis and ten of extrahepatic portal obstruction) have been analyzed.

3. Portacaval shunts appear to be of doubtful value and produce at best a temporary benefit. There is evidence to indicate that even partial deviation of the portal flow may impair liver function.

4. Further experience is necessary before proper evaluation of this operation can be made.

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(*See Discussion on page* 605)

THE MANAGEMENT OF CIRRHOSIS OF THE LIVER AND ASCITES WITH PARTICULAR REFERENCE TO THE PORTACAVAL SHUNT OPERATION

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A CERTAIN percentage of patients with cirrhosis of the liver and esophageal varices who are candidates for the portacaval shunt operation have ascites. The ascites is of varying duration and degree and presents a problem in management for early stabilization or diminution so that operation may be undertaken. The problem of hemorrhage from varices in some of these patients with ascites has been met by the group at this hospital[1] through the use of suture of the esophageal varices[2] or esophageal balloon tamponade. This allows sufficient time for improvement of the patient's general condition and liver function, and for stabilization of ascites in preparation for the portacaval shunt.

The formation of ascites in hepatic cirrhosis is a complex process representing so-called "decompensation." The several factors involved in its formation are believed to be (1) portal hypertension, (2) lowered osmotic pressure secondary to decreased serum-albumin level, (3) disturbances in the metabolism of sodium and water, and (4) an abnormal hormonal state. The relative importance of these factors must vary with each patient.

Probably all patients with cirrhosis and ascites have an elevation of portal pressure above the normal value of 100 to 125 mm. of water. While there are no methods for indirect measurement, Kunkel and associates[3] ascribed a high degree of portal obstruction to those patients with marked ascites with little or no edema and a minor degree to those with large amounts of edema and with less ascites forming slowly. In an analysis[4] of 118 patients with cirrhosis operated on at the Presbyterian Hospital for a shunting procedure, 41.5 per cent had ascites as an operative or preoperative clinical finding. Portal pressure measurements at operation varied between 200 and 600 mm. of water. The mean reading in the group without ascites was 400 ± 90 mm. of water and in those with ascites (minimal to severe) it was 370 ± 30 mm. of water. From an analysis of our data, there appears to be no correlation between the degree of portal pressure and ascites, regardless of its severity. While portal hyper-

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**Fellow Dazian Foundation.

tension is probably a factor in the formation of ascites its role must be minor, as witnesss the majority of patients with cirrhosis and portal hypertension without ascites.

There are many reports[5-11] dealing with the documentation of lowered serum albumin in patients with cirrhosis and ascites and dealing with the results obtained by replacement therapy. It was established[5, 6] that the serum-albumin level could be brought to normal temporarily by the intravenous use of human serum albumin, but the response to such treatment, gauged in terms of diuresis with loss of ascites and edema, was variable from patient to patient. There is agreement that patients with ascites of short duration and very low serum-albumin levels respond best to this therapy while those with long-standing ascites are usually resistant even with much larger doses over longer periods of time. Kunkel and associates[3] were able to rid fourteen of fifteen patients of ascites with varying amounts of albumin and they suggested that the resultant improved appetite and increased dietary intake might be more important than any direct osmotic effect. Faloon and associates[8] emphasized in their findings that albumin is of more benefit if used in conjunction with a low-sodium diet, for then paracenteses may be avoided allowing for a conservation of both the patient's albumin and the administered albumin. They reported the complications of fatal hemorrhage from esophageal varices in three patients and bleeding from a duodenal ulcer in another, coincident with or shortly following albumin administration. Its use in elderly or cardiac patients was considered dangerous. It would appear that this is a rather expensive form of therapy which is wasteful if repeated paracentesis is continued and unnecessary if a low-sodium diet is employed. Its use is, however, indicated to restore normal osmotic relationships when the ascites is stabilized or reabsorbed, particularly when operation, such as a portacaval shunt, is contemplated.

Many authors[7, 12-16] have established the fact that the single most important aspect of management in the stabilization or reabsorption of ascites is a rigid low-sodium diet. It is recognized that those patients with ascites excrete sodium in the urine poorly or not at all, thus accumulating 1 L. of abdominal fluid for each 120 to 140 meq. of sodium retained. Farnsworth and Krakusin[17] noted that the urinary electrolyte pattern in hepatic cirrhosis and massive ascites was similar to that in cardiac failure, with the retention of sodium and water being more marked in the former patients. Farnsworth[18] concluded that the renal tubules were playing a role in the retention of sodium, a fact which had not been considered in earlier theories. Her patients exhibited urinary suppression of sodium, regardless of daily salt ingested, and refractoriness to diuretic treatment. Renal function as determined by mannitol and para-aminohippurate clearances was somewhat reduced, while urinary electrolytes other than sodium showed normal responses to variable intake.

The findings of other investigators[19, 20] support Farnsworth's report of decreased renal function, while those of Epstein and associates[21] are at variance. The latter group demonstrated normal renal-function studies and concluded that the renal retention of sodium could be ascribed solely to increased tubular reabsorption.

Faloon and associates[7] noted the small quantities of sodium in the urine regardless of either the quantity administered or the route of administration, while Goodyer and associates[22] documented the striking difference in excretion of sodium in normal and cirrhotic persons without ascites as compared to cirrhotic patients with ascites. Others[23, 24] have added evidence to support all these findings.

It is clear that patients with cirrhosis without ascites behave more like normal persons in regard to urinary excretion of sodium. Those with ascites excrete sodium poorly or not at all as the result of increased tubular reabsorption and, in some, diminished renal function.

Rowntree,[25] in 1925, suggested that a low fluid, low sodium (0.49 Gm. of sodium) intake was of more importance than mercurial diuretics. Patek[26, 27] documented the value of a nutritious high-vitamin diet for the treatment of alcoholic cirrhosis which has become the basis of all dietary management. Layne and Schemm[12] reported excellent results with the use of a high fluid intake and low-sodium acid-ash diet in the management of patients with cirrhosis and ascites. Ammonium chloride, dilute hydrochloric acid by mouth, and mercurials were used in conjunction with the diet. Chalmers and Davidson,[14] in 1949, pointed out that a diet containing less than 1.5 Gm. of sodium chloride (25.5 meq. of sodium) resulted in little retention of fluid in the abdomen, since the extrarenal loss of sodium chloride had been shown to be approximately 1 Gm. per day under moderate temperature conditions.[28] Faloon[7] recommended a high-protein, high-calorie diet containing 21 meq. of sodium and Eisenmenger[15] recommended 0.8 to 1.2 Gm. of sodium chloride per day (14 to 20 meq. of sodium). The latter author found that four of twelve patients with cirrhosis and long-standing ascites who had resorbed the ascites on this low sodium intake were able to tolerate a normal salt intake after three months' restriction without reaccumulation, while the remaining eight reformed ascites on the high intake of salt. Gabuzda and associates,[23] in 1950, reported increased urine volumes when daily fluid intake was constant and the patient's sodium intake was changed from a high (113 meq. of sodium) to a low (10 meq. of sodium) one. They suggested that large quantities of body sodium were lost by repeated paracentesis leading to hyponatremia and a reduction of plasma volume, all three factors acting as stimuli for the renal conservation of sodium.

Thus, it is clear that a rigid low-sodium diet must be employed if the accumulation of ascites is to be stopped and that the amount of sodium retention determines the rate of accumulation.

In 1945, Ralli and co-workers[29] reported that the urine of patients with cirrhosis and ascites had a much higher concentration of antidiuretic substance than that of normal subjects or cirrhotic patients without ascites. Others[19, 30] have reported similar findings. On the other hand, Van Dyke and associates[31] studied the urine, for antidiuretic substance, of seven normal subjects and forty-four cirrhotic patients, one-half of whom had ascites. The urine of 50 per cent of those with ascites and 35 per cent of those without ascites showed antidiuretic activity, while none was detected in the normal

subjects. Higher titers were found in the urine of those with ascites. They concluded that antidiuretic substance was probably of minor importance, if any, in the production of ascites. It is apparent that the evidence obtained from several investigators is at variance.

Many patients with cirrhosis and ascites, referred to the Presbyterian Hospital for possible portacaval shunt operation, proved to have difficult problems in management on the general ward or private service. It was decided to admit a selected few to the metabolism ward, and this report concerns itself with an appraisal of fifteen patients. All patients were on water- and electrolyte-balance studies and most were on nitrogen-balance studies.

Water balance was recorded from the daily measured intake and output and daily weight, estimating insensible loss. Sodium and potassium values for all fluids and stool were determined by means of a flame photometer with the internal standard lithium[32] and chlorides by the method of Schales and Schales.[33] Electrolyte values in the stool, including those containing resin, were determined from the clear colorless fluid remaining after two- to four-day pooled specimens were homogenized and an aliquot was digested with concentrated sulfuric and nitric acid in a micro-Kjeldahl burner. Nitrogen intake and output were both calculated and analyzed for the diet and also for content in the urine and stool.[34] Blood volume determinations were performed with Evans blue dye (T 1824) according to the method of Gregersen,[35] and carbon-dioxide content was determined by the Van Slyke apparatus.[36] As part of a study to be reported later, total body-water values were obtained with a tracer of the stable isotope deuterium oxide[37] and sodium mass with Na^{24}.[38] Extracellular volumes were calculated from the space measured with sodium thiosulfate[39] which contained 85 meq. of sodium per 11.7 Gm. in 100 c.c. used for each test. This amount of sodium has been included in the balance figures.

Diet.—It may be seen that the dietary intake of sodium was variable (Table VII) in the early part of the study because we desired to supply a nutritious high-protein diet to patients with a poor appetite. It became apparent that accumulation of ascites continued on a moderate intake of sodium and could be stabilized only when a rigid restriction was imposed. In order to achieve this low-sodium, high-protein diet, it was necessary to resort to the several commercially available whole-protein and amino acid supplements, such as Protinal Powder,* Lonalac,† Lesofac,‡ and Stuart Amino Acids.§ The diets finally adopted are shown in Tables I to III. Table I outlines a diet for a patient with a small appetite; Table II, a good appetite; and Table III, the diet eaten on one day by Patient J. G. The amount of water ingested daily along with a low sodium intake of 9 to 12 meq. does not appear to be important in the formation of ascites. These diets are palatable and acceptable to patients and must be eaten if the patient is to improve and recover from ascites. It cannot be

*The National Drug Company.
†Mead Johnson and Company.
‡Wyeth Incorporated.
§The Stuart Company.

TABLE I. LOW-SODIUM DIET FOR PATIENTS WITH CIRRHOSIS OF THE LIVER AND ASCITES: SMALL APPETITE

FOOD	AMOUNT (GM.)	PROTEIN	FAT	CARBOHYDRATES	CALORIES	H_2O	Na
Orange juice	200	1.8		20.2	88.0		.02
Dextrose	30			30.0	120.0		.01
Lonalac	25	6.6	7.0	9.5	127.4		.14
Water	175						
Coffee	1.5 cups						
Sugar	20			20.0	80.0		
Heavy cream	30	.7	10.5	1.0	101.1		.42
Eggs (2)	100	12.8	11.5		155.0		3.52
Chocolate drink:							
Chocolate syrup	40	1.4	2.4	19.6	104.2		1.04
Lonalac	50	13.2	14.0	19.0	254.8		.29
Water	120						
Dextrose	40			40.0	160.0		.02
Lesofac	20	10.0	.2	7.8	74.0		
Heavy cream	30	.7	10.5	1.0	101.1		.42
Eggnog							
Egg yolk	50	8.2	16.0		176.0		.57
Egg white	50	5.4			21.5		2.39
Dextrose	40			40.0	160.0		.02
Lonalac	25	6.6	7.0	9.5	127.4		.14
Lesofac	20	10.0	.2	7.8	74.0		
Heavy cream	30	.7	10.5	1.0	101.1		.42
Water	125						
Grape juice	200	0.6		34.6	140.0		.08
Dextrose	40			40.0	160.0		.02
Stuart Amino Acids	60	49.7			198.8		
Water	300						
Sirloin steak	100	22.5	13.0		207.0		2.21
Total		150.9	102.8	301.0	2731.4		11.73

overemphasized that the patient's refusal to eat results in failure of the entire plan of management.

There have been many reports[7, 12-14, 17, 25, 40-42] dealing with the urinary excretion of sodium as the result of the use of mercurial diuretics with and without ammonium chloride in patients with hepatic cirrhosis and ascites. Some patients with ascites appear to retain the ability to excrete sodium in the urine, and in these the amount excreted is augmented by the use of mercurial diuretics and further enhanced by the addition of 3 to 4 Gm. of ammonium chloride daily for several days prior to an injection of the mercury salt. In others, who excrete sodium in small amounts, the response to this regimen is variable and often the net long-term effect is negligible, if any, a short-term gain being canceled out in the ensuing few days. Patients who are forming ascites at a maximal rate excrete less than 1 meq. of sodium in the urine daily and this amount is apparently not increased by the use of diuretics. There is agreement that the serum-sodium level is not an important aspect of the response to diuretics. All observers have noted the much greater output of chloride ion in the urine as compared with sodium ion under varying conditions with the use of the diuretic salts. Hilton[42] called attention to the increased urinary excretion of potassium following the use of mercurial diuretics in patients with cirrhosis and ascites, and he observed that the loss (maxi-

TABLE II. LOW-SODIUM DIET FOR PATIENTS WITH CIRRHOSIS OF THE LIVER AND ASCITES: GOOD APPETITE

FOOD	AMOUNT (GM.)	PROTEIN	FAT	CARBOHYDRATES	CALORIES	H_2O	Na
			Breakfast				
Orange juice	200	1.8		20.2	88.0	85.7	.02
Dextrose	20			20.0	80.0	2.0	.01
Salt-poor toast	60	5.0	1.7	31.8	162.3	21.0	
Salt-poor butter	10	0.1	8.1		73.3	1.6	.02
Grape jelly	10			7.5	30.1	3.4	.04
Sugar	10			10.0	40.0		
Milk	50	1.8	2.0	2.4	34.5	43.5	1.00
Heavy cream	30	0.7	10.5	1.0	101.1	17.7	.42
Coffee	150						
			Lunch				
Ground beef	200	38.2	26.0		386.8	134.0	4.44
Potato	100	2.0	0.1	19.1	85.0	77.8	.03
Salt-poor bread	40	3.3	1.1	21.2	108.2	14.0	
Salt-poor butter	10	0.1	8.1		73.3	1.6	.02
Ice cream							
Strawberry	50	0.4	0.3	4.0	20.5	45.0	.02
Lonalac	5	1.3	1.4	1.9	25.5	0.1	.03
Dextrose	20			20.0	80.0	2.0	.01
Lesofac	10	5.0	0.1	3.9	37.0	0.4	
			Dinner				
Sirloin steak	200	45.0	26.0		414.0	134.0	4.42
Salt-poor peas	70	2.4	0.2	4.8	30.1	59.8	
Salt-poor bread	40	3.3	1.1	21.2	108.2	14.0	
Orange juice	150	1.4		15.2	66.0	128.6	.02
Dextrose	15			15.0	60.0	1.5	.01
Ice cream							
Fresh strawberry	100	0.8	0.6	8.1	41.0	90.0	.04
Dextrose	40			40.0	160.0	4.0	.02
Lonalac	5	1.3	1.4	1.9	25.5	0.1	.03
Lesofac	20	10.0	0.2	7.8	74.0	0.8	
*Stuart Amino Acids	60	49.7			198.8		
Total		173.6	88.9	277.0	2577.7		10.60

*20 at each meal.

mum 250 meq. of potassium in a 24 hour urine) may be sufficient to produce symptomatic hypokalemia. The clinical syndrome of weakness, drowsiness, prostration, anorexia, and cardiac arrhythmias attributed to hyponatremia was identical to that seen with hypokalemia.

Our experience parallels that of others in that we also obtained a variable output of urinary sodium with diuretics. It may be seen in Table IV that Patient C. S., on a daily dietary intake of 26 to 27 meq. of sodium employed after a portacaval shunt operation and the development of ascites, had an excellent output of sodium in the urine on three successive days following the use of 2 c.c. of Mercuhydrin each day. The same is true of Patient F. N. (Table V) who received ammonium chloride in addition to the Mercuhydrin while having a daily dietary intake of 24 meq. of sodium. However, Patient M. S. (Table VI), who was forming ascites at a rapid rate, demonstrated no response to three doses of Mercuhydrin given on alternate days with a daily dietary intake of 14 to 21 milliequivalents.

TABLE III. LOW-SODIUM DIET FOR PATIENTS WITH CIRRHOSIS OF THE LIVER AND ASCITES (PATIENT, J. G., AGED 16 YEARS, UNIT NO. 099485)

FOOD	AMOUNT (GM.)	PROTEIN	CALORIES	Na
		Breakfast		
Orange juice	200	1.8	88.0	.02
Dextrose	20		80.0	.01
Salt-poor toast	80	6.6	216.4	
Salt-poor butter	20	0.1	146.6	.04
Sugar	10		40.0	
Tea				
		Lunch		
Ground-beef patty	200	38.2	386.8	4.44
Salt-poor bread	40	3.3	108.2	
Salt-poor butter	10	0.1	73.3	.02
Peaches, canned	50	0.6	112.5	.33
Ice cream				
Strawberries	50	0.4	20.5	.02
Heavy cream	30	0.7	101.1	.42
Dextrose	20		80.0	.01
		Dinner		
Sirloin steak	200	45.0	414.0	4.42
Salt-poor bread	40	3.3	108.2	
Salt-poor butter	10	0.1	73.3	.02
Orange juice	150	1.4	66.0	.02
Dextrose	20		80.0	.01
Ice cream				
Strawberries	100	0.8	41.0	.04
Dextrose	40		160.0	.02
Lonalac	5	1.3	25.5	.03
Lesofac*	20	10.0	74.0	
Stuart Amino Acids*	60	49.7	198.8	
Total		163.4	2694.2	9.90

*Dry weight.

Portis and Weinberg[43] recently emphasized the value of dextrose therapy in the treatment of cirrhosis of the liver and obtained excellent responses of diuresis in patients with ascites using hypertonic solutions of dextrose. While we have had no experience with this method of producing an osmotic diuresis, the results could be anticipated to be of the same order of magnitude as that obtained with mercurials.

As indicated, cessation of the ascites has been accomplished with a low-sodium diet alone by many workers. Some investigators[45, 48, 49] have suggested that a higher sodium intake in the diet might be combined with ion-exchange resin, resulting in a similar net effect. This would obviate the need for a special diet somewhat difficult to prepare, and allow for more palatable foods for those patients with mild-to-moderate anorexia. In 1946, Dock[44] suggested the use of ion-exchange resins for withdrawing sodium from the body through increased fecal excretion. Details of studies evaluating the chemistry and pharmacology of exchange resins may be found in the excellent papers of Danowski and associates.[46, 47] The carboxylic cation-exchange resins are commercially available in the hydrogen, ammonium, sodium, and potassium forms individually or in various combinations. The hydrogen and ammonium forms, while allowing for the withdrawal of sodium and potassium by exchange,

TABLE IV. THE RESPONSE* TO MERALLURIDE SODIUM† IN PATIENTS WITH CIRRHOSIS AND ASCITES ON LOW-SALT DIET (C. S., PORTACAVAL SHUNT, JUNE 9, 1950)

POST-OPERATIVE DAYS	DOSAGE OF MERALLURIDE SODIUM† (C.C.)	SERUM Na (MEQ. PER LITER)	SODIUM			CHLORIDE			URINE OUTPUT (C.C.)	WEIGHT (KG.)
			IN	OUT	BALANCE	IN	OUT	BALANCE		
22-23	0	134	27	4	+23	39	13	+26	1,150	56.8
24	2	131	26	67	−41	38	89	−51	1,720	57.0
25	2		26	36	−10	38	65	−27	1,850	56.5
26	2		26	56	−30	38	70	−32	1,450	56.4
27	0		26	8	+18	38	2	+36	1,750	56.0

*All figures represent daily averages.
†Mercuhydrin (Lakeside Laboratories, Inc.).

TABLE V. THE RESPONSE* TO MERALLURIDE SODIUM† IN PATIENTS WITH CIRRHOSIS AND ASCITES ON LOW-SALT DIET (F. N., PORTACAVAL SHUNT, JUNE 13, 1951)

PREOPERATIVE DAYS	THERAPY		SERUM Na (MEQ. PER LITER	SODIUM			CHLORIDE			URINE OUTPUT (C.C.)	WEIGHT (KG.)
	MERALLURIDE SODIUM† (C.C.)	NH_4Cl (GM.)		IN	OUT	BALANCE	IN	OUT	BALANCE		
21-17	0	0	144	24	7	+17	32	13	+19	1,067	87.7
16	2	3	142	24	21	+3	88	253	−165	2,290	87.8
15	0	3	142	24	7	+17	88	22	+66	1,420	86.7
14	2	3	142	24	75	−51	88	138	−50	1,900	87.3
13	0	3	142	24	3	+21	88	98	−10	1,120	86.8
12	2	3	140	24	65	−41	88	136	−48	2,330	87.3
11	0	3	140	24	0	+24	88	3	+85	1,460	86.6
10-6	0	0	141	24	5	+19	32	29	+3	1,440	87.1
5	2	3	140	24	37	−13	32	137	−105	2,500	86.5
4-2	0	0		37	16	+11	32	59	−27	1,400	87.0

*All figures represent daily averages.
†Mercuhydrin (Lakeside Laboratories, Inc.).

TABLE VI. THE RESPONSE* TO MERALLURIDE SODIUM† IN PATIENTS WITH CIRRHOSIS AND ASCITES ON LOW-SODIUM DIET (M. S., NO SURGERY)

TIME IN HOSPITAL (DAYS)	DOSAGE OF MERALLURIDE SODIUM† (C.C.)	SERUM Na (MEQ. PER LITER)	SODIUM			CHLORIDE			URINE OUTPUT (C.C.)	WEIGHT (KG.)
			IN	OUT	BALANCE	IN	OUT	BALANCE		
29-32	0		21	2	+19	38	7	+31	1,182	58.0
33	2	133	18	4	+14	38	28	+10	1,290	58.5
34	0	129	18	2	+16	38	11	+27	1,140	58.4
35	2		18	0	+18	38	32	+6	1,400	58.4
36	0	131	16	6	+10	35	14	+21	850	58.1
37	2		18	0	+18	38	16	+22	1,130	58.5
38-39	0	138	14	1	+13	33	1	+32	1,204	58.6

*All figures represent daily averages.
†Mercuhydrin (Lakeside Laboratories, Inc.).

result in an acidosis similar to that following the use of ammonium chloride, and may have a beneficial effect in patients without impaired renal function. However, the loss of potassium through the stool may result in chemical and clinical hypokalemia, thus further complicating the acidosis produced by absorption of hydrogen and ammonium ions. When given by mouth in divided doses up to 60 Gm. per day, the efficiency is approximately 1 meq. of sodium removed per gram of resin when the diet contains a moderate

or liberal amount of sodium,[48] and approximately 50 per cent more potassium is lost than sodium. When sodium is rigidly limited in the diet, the efficiency of the resin is correspondingly reduced. A daily intake of more than 60 Gm. of resin may lead to nausea.

In order to prevent chemical and clinical hypokalemia while removing sodium, compositions of resins have been made containing a certain percentage of potassium. As expected, this too leads to a decreased efficiency of sodium removal but results in a less acidifying effect. In addition, anion-exchange resin may be incorporated in the mixture to diminish further the production of acidosis.

Martz, Kohlstaedt, and Helmer[45] reported their evaluation of eleven patients with cardiac decompensation and five with advanced cirrhosis given resins by mouth in an attempt to deplete the sodium content of body fluids. The use of the acid form of resin resulted in hypokalemia which was prevented subsequently by the addition of a potassium form of the resin. The acid-and-potassium form led to a reduction in carbon-dioxide content of the blood in some patients with impaired renal function requiring cessation of this therapy, while the subsequent addition of small amounts of anion-exchange resin eliminated this undesirable effect. A diet containing 1.5 to 3 Gm. of sodium per day was allowed and the resin given in 60 Gm. daily amounts of four divided doses.

Moser and associates[49] studied eight patients with cirrhosis and ascites on a diet containing 1 to 3 Gm. of sodium with the addition of 30 to 70 Gm. of resin daily (Carbo-Resin,* sodium-removing resin). The ascites was controlled readily with the use of resins in all patients and it reappeared in one patient on a diet containing 1.5 Gm. of sodium after the resin was discontinued. It was subsequently reabsorbed when the resins were given a second time. Moser and associates emphasized the possible development of diminished plasma carbon-dioxide content and acidosis and the development of symptomatic hypokalemia in two patients who responded to treatment with potassium salts. They also stressed that the patient's ability to follow a prescribed diet was an important requisite of resin therapy.

Gabuzda and associates,[50] in 1952, reported severe toxic reactions with the use of various forms of resins in twelve patients with cirrhosis, ascites, and edema who were given a low- or normal-sodium diet. Four patients treated with the ammonium resin in doses of 20 to 30 Gm. three times each day for

CHART 1

COMPOSITION OF CARBO-RESIN (LILLY)	
Alkylene polyamine resin (anion-exchange)	12 per cent
Potassium salt of carboxylic-acid resin (cation-exchange)*	29 per cent
Carboxylic-acid resin (cation-exchange)	59 per cent
COMPOSITION OF RESODEC (SMITH, KLINE & FRENCH)	
Polycarboxylic cation exchange compound in NH_4 and K form:	
K form	22 per cent
NH_4 form	78 per cent

*1.3 meq. of potassium ion per gram of resin.

*Eli Lilly & Company.

from three to thirteen days obtained a diuresis with diminution of ascites and edema. Three of the four developed mental confusion and disorientation along with a tremor which cleared on cancellation of the resins. Three of four patients who received hydrogen cation-exchange resin in doses of 45 to 80 Gm. daily for from nine to twelve days had a diuresis with a moderate-to-marked loss of body weight. Two patients developed marked chemical and clinical hypokalemia. Three of four patients receiving 30 to 90 Gm. of the ammonium-potassium resin daily for from three to twelve days also had a decrease in ascites and edema. Untoward effects encountered in all four were similar to those in patients receiving the ammonium resin. The mental picture in all of these patients was similar to that seen in patients with impending hepatic coma. These authors concluded that the ion-exchange resins investigated were poorly tolerated by patients with severe liver disease and should be administered cautiously, if at all. A rigid low-sodium diet was still the best method of management for ascites and edema and was not replaced by resins.

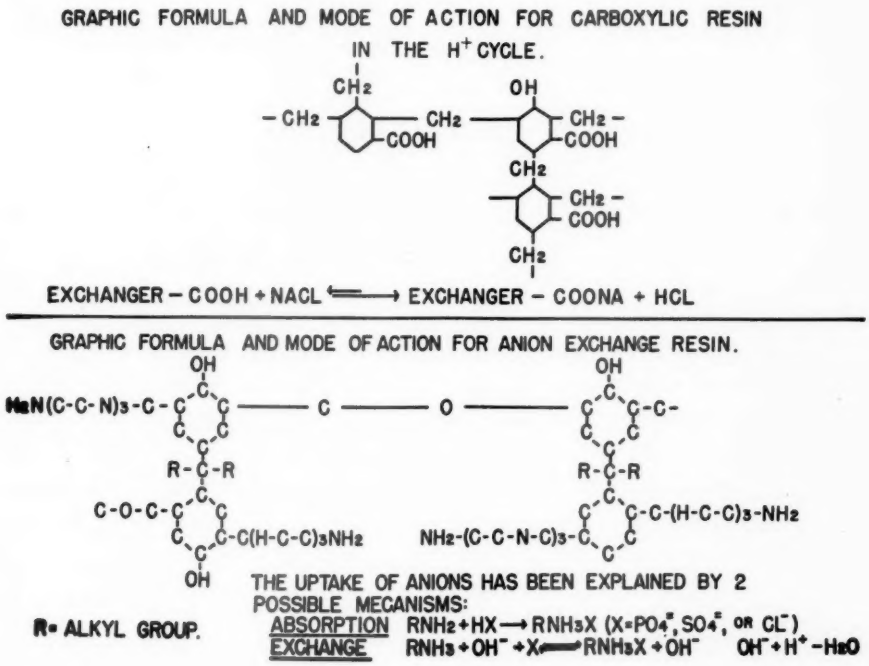

GRAPHIC FORMULA AND MODE OF ACTION FOR CARBOXYLIC RESIN
IN THE H+ CYCLE.
EXCHANGER – COOH + NACL ⟷ EXCHANGER – COONA + HCL
GRAPHIC FORMULA AND MODE OF ACTION FOR ANION EXCHANGE RESIN.
R= ALKYL GROUP.
THE UPTAKE OF ANIONS HAS BEEN EXPLAINED BY 2 POSSIBLE MECANISMS:
ABSORPTION RNH2+HX⟶RNH3X (X=PO4=, SO4=, OR CL-)
EXCHANGE RNH3+OH-+X⟷RNH3X+OH- OH-+H+-H2O

Fig. 1.

The program of evaluating the use of ion-exchange resins in conjunction with a low-sodium diet for patients with cirrhosis and ascites was initiated by us in 1951. Resodec* was used at the outset and subsequently Carbo-Resin† was used, since there appeared to be a slightly higher degree of patient tolerance for the latter preparation in comparable dosage.

The composition of these resins may be seen in Chart 1 along with the percentage of each ingredient. Fig. 1 shows a graphic formula and mode of

*Supplied by Smith, Kline & French Laboratories.
†Supplied by Eli Lilly & Company.

TABLE VII. SUMMARY OF RESULTS IN FIFTEEN PATIENTS

PATIENT	AGE (YR.)	DURATION OF ASCITES	PERIOD ASCITES MANAGED		FREQUENCY OF PARACENTESIS	OPERATION*	MERCUHYDRIN	I. V. ALB. (GM.)	TIME REQUIRED TO STABILIZE AND DIMINISH ASCITES†	GRADE OF ASCITES‡ BEFORE STUDY
			PRE-OP.	P. O.						
M. I.	45	2 yr.		+	None	Splenorenal shunt			21 days	I
F. N.	59	3 mo.	+		None	Portacaval shunt	+		Stabilized on admission	II
J. E.	39	1 mo.		+	None	Portacaval shunt	+	250	3 wk.	III
C. S.	48	9 mo.		+	Once	Portacaval shunt	+		1 wk.	II
D. F.	61	5 mo.	+		5-6 wk.	None	+	500	Not stabilized	III
M. M. S.	43	9 mo.			4 wk.	None	+	150	Not stabilized	III
M. I. S.	43	3 mo.	+		3-4 wk.	Portacaval shunt	+	50	Not stabilized	III
P. B.	68	5 mo.	+		2-3 wk.	None	+		Not stabilized	III
L. C.	59	1 yr.		+	Weekly	Portacaval shunt	+	550	1 wk.	III
I. N.	19	6 mo.	+	+	Weekly	Splenectomy	+	475	14 mo.	III
			Patients Treated With Exchange Resins.							
J. G.	16	3 yr.	+		Weekly	Splenectomy		125	7 days	III
L. B.	48	3.5 yr.	+		2 wk.	Portacaval shunt			19 days	III
C. M.	52	7 mo.	+		Once	Portacaval shunt		575	15 days	III
H. L.	54		+	+	2 wk.	Splenorenal shunt		50	26 days	III
M. R.	37	7 mo.	+		Weekly	Ligation of varices			Not stabilized	III

action[51] for both a cation- and anion-exchange resin as contained in Carbo-Resin. The inclusion of 12 per cent anion exchanges affects the fecal phosphate excretion primarily and the sulfate and chloride excretion to a lesser extent. The potassium cycle of carboxylic resin contains at least 5.5 meq. of potassium ion per gram of resin and when it is included in Carbo-Resin as 29 per cent of the mixture there is 1.3 to 1.7 meq. per gram. The figure of 1.3 meq. of potassium per gram of Carbo-Resin has been included in the balance data.

Results.—A total of fifteen patients has been studied (Table VII) for the past three years. All had cirrhosis with ascites of varying severity and in some the ascites appeared following operation without being present preoperatively. The diagnosis was established by biopsy in twelve patients and with chemistry studies in the remaining three. One patient (M. I.) was studied while on a low-sodium diet alone, and nine patients were studied while on a variable sodium intake with the addition of mercurials; of these, six had albumin. Finally, five patients had the combination of low-sodium and ion-exchange resin.

It may be seen in the table that Patient M. I., studied while receiving a low-sodium diet alone, was able to excrete sufficient sodium in the urine to

ON METABOLIC BALANCE WITH CIRRHOSIS AND ASCITES

GRADE OF ASCITES‡ BEFORE STUDY	GRADE OF ASCITES‡ END STUDY	SERUM ALBUMIN§ BEFORE STUDY	SERUM ALBUMIN§ END STUDY	PATIENTS WITH TWO STUDIES	AVERAGE DAILY SODIUM IN DIET	IN TOTAL	OUT PAR.	OUT URINE	OUT STOOL	OUT TOTAL‖	BALANCE¶	COMPLETE BALANCE
I	None	4.2	3.5		20.6	27.8	0	38.9	0	38.9	−11.1	−11.1
II	II	4.0	3.5		21.4	25.0	0	17.0	0	17.0	+8.0	+8.0
II	II	3.7	3.3	Study I	25.8	38.0	0	60.4	4.2	64.6	−26.6	−26.6
III				Study II	46.3	60.5		21.0	0.9	25.3	+35.2	+35.2
	None	4.1	3.7		26.5	26.5	0	29.4	0	29.4	−2.9	−2.9
II	III	1.8	3.0		28.5	43.3	64.1	0.7	0	64.8	+42.6	−21.5
	III	2.9	3.5		19.6	29.4	43.2	4.4	0	47.6	+25.0	−18.2
III	III	3.1	—		18.8	28.3	87.3	19.1	0	106.4	+9.2	−78.1
III	III	2.6	—		27.6	43.0	0	2.8	0	2.8	+40.2	+40.2
III	II	4.1	5.0		53.7	66.4	0	92.9	0	92.9	−26.5	−26.5
	None	1.9	3.3	Study I	35.3	49.2	91.5	6.3	0	97.8	+42.9	−48.6
III				Study II	22.1	22.1	—	12.2		12.2	+9.9	+9.9
III	II	2.5	2.6		10.2	30.9	0	53.9	40.3	94.2	−63.3	−63.3
III	II	3.7	4.5		10.5	17.0	50.0	1.0	5.9	57.1	+9.9	−40.1
	II	2.5	2.5		12.6	13.3	6.3	3.7	17.5	27.5	−7.9	−14.2
	II	2.0	4.5		13.8	29.5	5.8	3.7	11.8	21.3	+14.0	+8.2
III	III	3.1	2.9		13.2	59.8	44.1	0.2	11.9	56.1	+47.7	+3.7
III												
III												
III												
III												

*S.R. represents splenorenal shunt; P.C., portacaval shunt.
†After admission to surgical metabolism ward.
‡I represents 250 to 1,000 c.c. of ascites; II, 1 to 5 L; and III, more than 5 liters.
§Determined at the beginning and end of the study in the metabolism ward.
‖Includes sodium intake in diet plus any quantity resulting from the intravenous use of fluids such as albumin, electrolyte solutions, blood, and space determinations.
¶Excluding the amount of sodium removed by paracentesis.

achieve a significant negative balance. As expected this resulted in reabsorption of the slight amount of ascitic fluid which she had.

The use of mercurials in conjunction with a variable sodium intake resulted in a good diuretic response of sodium in five patients (F. N., C. S., M. I. S., P. B., I. N.) and a poor response in four (J. E., D. F., M. M. S., L. C.). Salt-poor human serum albumin was given to six patients in amounts shown in Table VII, resulting in a temporary elevation of serum albumin, but no increased excretion of sodium in the urine or diuresis.

While Patient F. N.'s ascites was stable on admission to the ward, it apparently did not increase as might be expected from the small positive balance, which does not take into account any loss through the skin. Three patients (J. E., C. S., L. C.) were able to stabilize the ascites within a one- to three-week period as the result of a negative sodium balance produced by adequate urinary excretion of sodium. The remaining six patients in this group received an amount of sodium either in the diet or otherwise which resulted in a positive balance. A complete sodium balance, including that amount removed from the body through paracentesis, changed from positive to negative for patients D. F., M. M. S., M. I. S., and I. N., but it is apparent that the formation of ascites was not controlled. It would seem that Patients D. F., M. M. S., M. I. S.,

and P. B. were candidates for a lower sodium intake or the use of ion-exchange resins.

The five patients treated with a rigid low-sodium diet and ion-exchange resins are presented in more detail.

J. G. (Fig. 2, Table VIII) was a 16-year-old male patient with a two-year history of ascites and ankle edema requiring four paracenteses for comfort in the month prior to admission to the hospital. No gastrointestinal bleeding had occurred.

Examination demonstrated marked ascites with a nonpalpable liver but with an enormous spleen (weight 2,210 Gm., recorded after removal) and 4 plus ankle edema.

Chemistry studies revealed a blood picture compatible with extreme hypersplenism, a prothrombin time of thirty seconds (normal 14), Bromsulphalein retention 38 per cent after thirty minutes, cephalin flocculation 4+, total serum protein 4.0 Gm. per cent, albumin 2.3 Gm. per cent, serum nonprotein nitrogen 30 mg. per cent (normal), bilirubin 1.1 mg. per cent. Esophageal varices were demonstrated by x-ray examination.

The patient was admitted to the metabolism ward on July 1, 1952, and placed on a high-protein and caloric diet containing 10 meq. of sodium ion. (Any sodium intake in excess shown in Fig. 2 resulted from space determinations or the use of albumin and blood.) The high potassium intake included the amount supplied in the diet, an additional 60 meq. per day received as potassium salts,* and the amount incorporated in the resins.

After a three-day period of control study, 45 Gm. of Carbo-Resin were given daily in 15 Gm. doses with meals. The extra potassium salts were given between meals.

It may be seen that a persistently negative sodium balance occurred along with a positive potassium balance and absorption of the ascites and edema, as witness the weight loss. No acidosis developed. A constant hypoalbuminemia is recorded throughout the study. In the week prior to operation, an increased urinary excretion of sodium occurred without a decrease in the efficiency of the resins. At operation, 6 L. of fluid were recovered from the abdomen, and following operation an enormous diuresis of sodium was recorded.

Table VIII shows that 1.3 meq. of sodium were removed per gram of resin ingested, and a like amount of potassium was excreted in the stool.

It is probable that a rigid low-sodium diet alone would have controlled this patient's ascites, but the resins proved efficient in creating a negative balance without chemical or clinical toxicity, thus leading to early operation. It is apparent that the enormous spleen played a role in the formation and persistence of ascites.

This patient has been followed for six months subsequent to operation on a moderately restricted sodium intake, and there has been no reaccumulation of ascites.

L. B. (Fig. 3, Table IX) was a 49-year-old man with alcoholic cirrhosis and ascites of three years' duration. Attempts to control the ascites with mercurials, low-sodium diet, and ion-exchange resins intermittently during that period met with failure. Paracenteses, removing 12 to 14 L., were performed every two weeks in the six months prior to the present admission.

Examination revealed a severe degree of ascites with a moderately enlarged liver and nonpalpable spleen. There was no ankle edema.

Chemistry studies showed a total serum protein of 6.1 Gm. per cent, albumin 3.7 Gm. per cent, cephalin flocculation negative, serum bilirubin 1.3 mg. per cent, serum nonprotein nitrogen 29 mg. per cent (normal), and a Bromsulphalein retention 7 per cent after thirty minutes. Esophagram and esophagoscopy failed to reveal any varices.

*Potassium Salts-Triplex, Eli Lilly & Company.

TABLE VIII. QUANTITATIVE REMOVAL OF SODIUM AND POTASSIUM PER GRAM OF RESIN (PATIENT J. G.)

PERIOD	NUMBER OF DAYS	RESIN*		SODIUM†				POTASSIUM†			
		DAILY (GRAMS)	TOTAL (GRAMS)	INTAKE PER ORUM	OUTPUT (URINE)	OUTPUT (STOOL)	MEQ. PER GM. RES. IN STOOL	INTAKE PER ORUM	OUTPUT (URINE)	OUTPUT (STOOL)	MEQ. PER GM. RES. IN STOOL
20-18 days preoperative	3	0	0	7.9	23.1	9.4	0	50.6	128.4	13.5	0
17-11 days preoperative	7	45	315	11.9	2.0	52.6	1.2	147.4	75.0	68.9	1.5
10-2 days preoperative	9	45	405	11.5	39.0	64.4	1.4	154.9	98.2	51.7	1.1
1-7 days postoperative	7	0	0	7.2	117.0	4.8	0	74.0	60.4	8.1	0

Total amount of resin 720 Gm.
Total stool sodium 947.8 meq. } 1.3 meq. sodium per gram of resin.

*Carbo-Resin, Eli Lilly & Company.
†Daily averages in total meq.

TABLE IX. QUANTITATIVE REMOVAL OF SODIUM AND POTASSIUM PER GRAM OF RESIN (PATIENT L. J. B.)

PERIOD (DAYS PREOPERATIVE)	NUMBER OF DAYS	RESIN* DAILY (GRAMS)	RESIN* TOTAL (GRAMS)	SODIUM† INTAKE PER ORUM	SODIUM† OUTPUT (URINE)	SODIUM† OUTPUT (STOOL)	SODIUM† MEQ. PER GM. RES. IN STOOL	POTASSIUM INTAKE PER ORUM	POTASSIUM OUTPUT (URINE)	POTASSIUM OUTPUT (STOOL)	POTASSIUM MEQ. PER GM. RES. IN STOOL
42-37	6	0	0	16.4	2.2	2.6	0	90.2	63.5	10.4	0
36-33	4	34	135	12.6	0	16.9	0.5	122.2	32.6	19.0	0.6
32-29	4	59	235	15.3	0	6.9	0.1	195.7	18.3	85.2	1.4
28-13	14	53	740	12.6	1.1	3.4	0.06	194.5	17.7	94.0	1.8
12-4	9	60	540	8.6	1.1	4.0	0.07	236.1	21.1	136.8	2.3
3-1	3	60	180	6.3	0	14.4	0.2	222.0	3.6	104.4	1.7

Total amount of resin 1830 Gm.
Total stool sodium 222 meq. } 0.12 meq. sodium per gram of resin

*Carbo-Resin, Eli Lilly & Company.
†Daily averages in total meq.

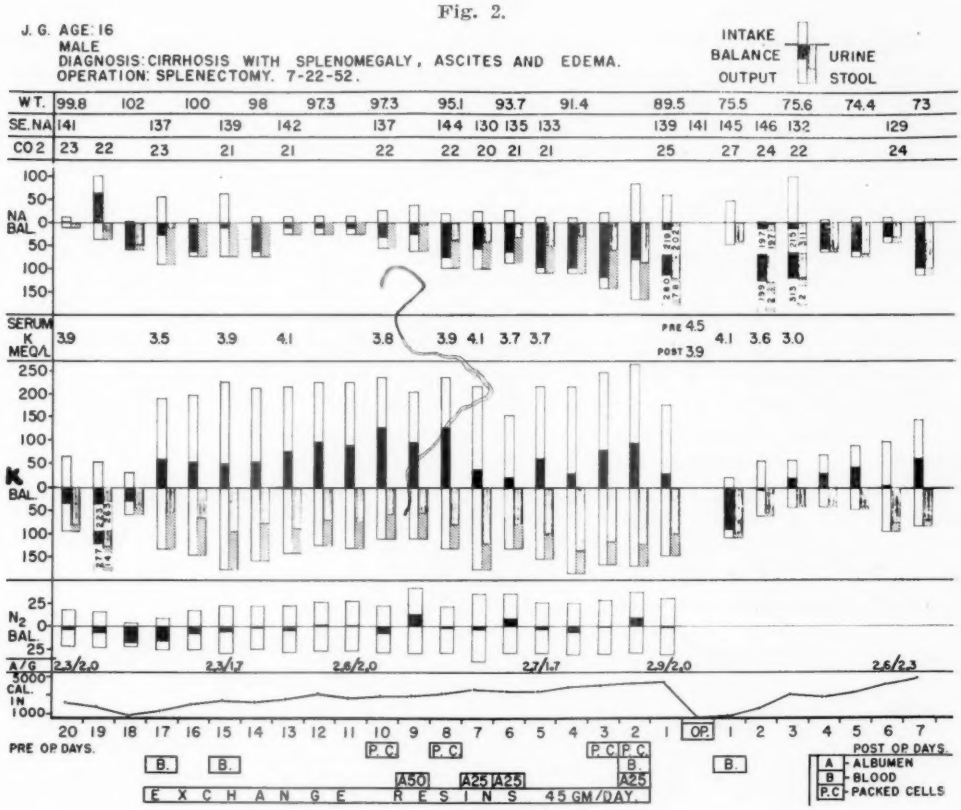
TABLE X. QUANTITATIVE REMOVAL OF SODIUM AND POTASSIUM PER GRAM OF RESIN (PATIENT C. M.)

PERIOD (DAYS PREOPERATIVE)	NUMBER OF DAYS	RESIN* DAILY (GRAMS)	RESIN* TOTAL (GRAMS)	SODIUM† INTAKE PER ORUM	SODIUM† OUTPUT (URINE)	SODIUM† OUTPUT (STOOL)	SODIUM† MEQ. PER GM. RES. IN STOOL	POTASSIUM INTAKE PER ORUM	POTASSIUM OUTPUT (URINE)	POTASSIUM OUTPUT (STOOL)	POTASSIUM MEQ. PER GM. RES. IN STOOL
61-58	4	45	180	No data				No data			
57-51	7	45	315	11.4	1.1	29.8	0.7	170.1	30.5	77.3	1.7
50-44	7	45	315	12.3	3.5	25.4	0.6	198.8	38.3	79.4	1.8
43-37	7	45	315	14.2	1.2	23.3	0.5	218.3	38.6	31.0	1.4
36-35	2	45	90	17.0	2.2	16.0	0.4	218.3	33.5	64.6	1.4
34-26	9	45	405	No data				No data			
25-20	6	45	270	12.5	0.4	1.0	0.02	239.2	49.0	75.1	1.7
19-8	12	45	540	No data				No data			
7-2	6	45	270	12.2	13.7	4.1	0.1	246.1	81.7	15.1	0.3

Total amount of resin 1575 Gm.
Total stool sodium 612 meq. } 0.4 meq. sodium per gram of resin

*Resodec, Smith, Kline & French Laboratories.
†Daily averages in total meq.

Fig. 2.


J. G. AGE: 16
MALE
DIAGNOSIS: CIRRHOSIS WITH SPLENOMEGALY, ASCITES AND EDEMA.
OPERATION: SPLENECTOMY. 7-22-52.
INTAKE
BALANCE
OUTPUT
URINE
STOOL
WT.
SE. NA
CO2
NA BAL.
SERUM K MEQ/L
PRE 4.5
POST 3.9
K BAL.
N2 BAL.
A/G
CAL. IN 1000
PRE OP DAYS.
POST OP DAYS.
B.
P.C.
A50
A25 A25
A25
EXCHANGE RESINS 45 GM/DAY.
A - ALBUMEN
B - BLOOD
P.C. - PACKED CELLS

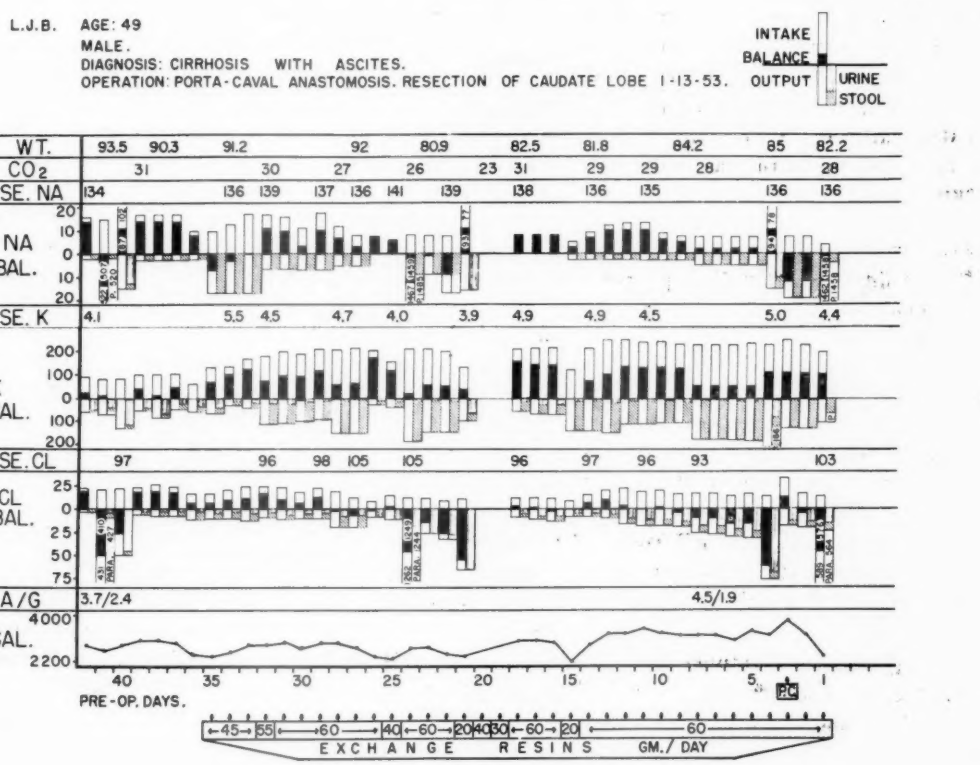

L.J.B. AGE: 49
MALE.
DIAGNOSIS: CIRRHOSIS WITH ASCITES.
OPERATION: PORTA-CAVAL ANASTOMOSIS. RESECTION OF CAUDATE LOBE 1-13-53.
INTAKE
BALANCE
OUTPUT
URINE
STOOL
WT.
CO2
SE. NA
NA BAL.
SE. K
K BAL.
SE. CL
CL BAL.
A/G
CAL.
PRE-OP. DAYS.
P.C.
EXCHANGE RESINS GM./DAY

Fig. 3.

The patient was admitted to the metabolism ward on Dec. 12, 1952, and was placed on a high-protein and calorie diet containing 15 meq. of sodium ion. Space determinations account for the higher intake of sodium noted in Fig. 3. A partial paracentesis removing only 4 L. was performed on the day of admission for the patient's comfort. Carbo-Resin was started, as indicated in Fig. 3, and the variable daily intake is recorded. A second paracentesis (11 L.) was performed on Dec. 20 prior to an attempt at hepatic vein catheterization and a third one (4.6 L.) was performed on the day immediately before operation. The last two paracenteses removed all fluid possible. Because of the slow accumulation of ascites and the low extraction of sodium in the stool, the dietary intake of sodium was reduced to 8 meq. on the twenty-seventh preoperative day. Table IX records the low efficiency of the resins as 0.12 meq. of sodium removed per gram of resin, which may have resulted from the greater withdrawal of potassium in the stool.

It is apparent that the slower accumulation of ascites occurred primarily from the use of a low sodium intake and that this was aided by a withdrawal of 222 meq. of sodium in the stool. No acidosis or toxicity developed during the study and the serum potassium remained normal. At operation, a large caudate lobe of the liver, believed to be causing pressure on the vena cava, was resected and a portacaval shunt was performed. Postoperatively, the patient was continued on a diet containing 8 meq. of sodium ion for the two and one-half weeks of hospital stay because of his failure to excrete sodium in the urine. No ascites was detectable clinically at the time of discharge.

C. M. (Fig. 4, *A* and *B*, Table X) was a 52-year-old man admitted to Presbyterian Hospital on Nov. 11, 1951, after a ten-month period of ascites and ankle edema requiring a single paracentesis prior to entry. There had been no gastrointestinal bleeding.

Examination revealed a greatly distended abdomen with no palpable organs and 3 plus ankle edema.

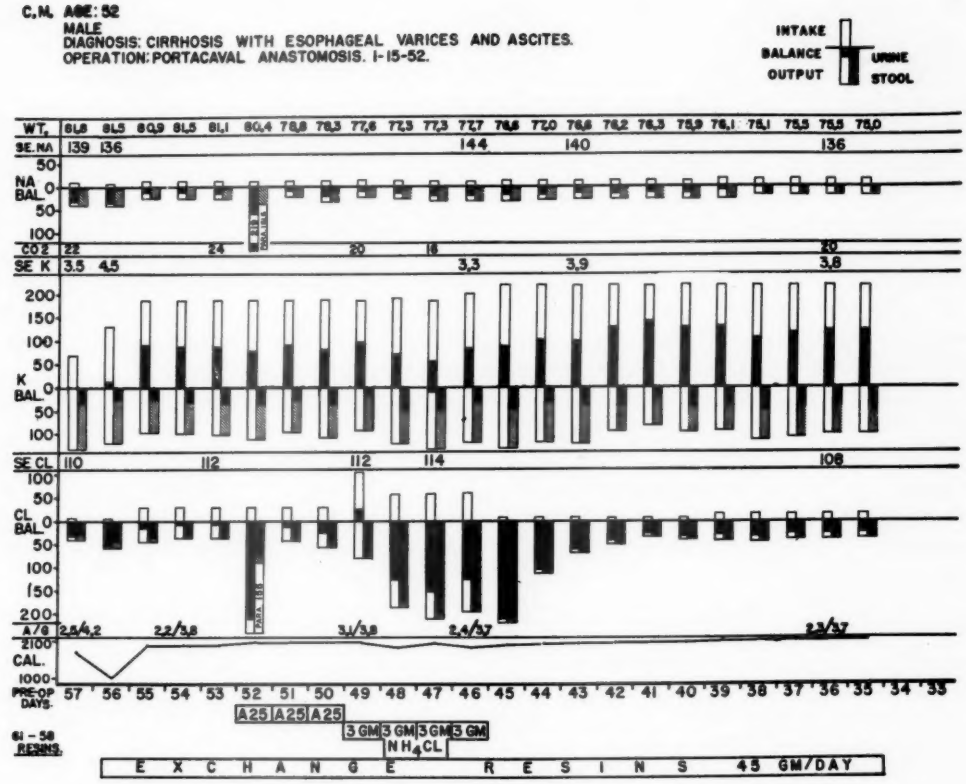
Chemistry studies showed a total serum protein of 5.8 Gm. per cent, albumin 2.5 Gm. per cent, cephalin flocculation 3+, Bromsulphalein retention 47 per cent at thirty minutes initially, and a second determination of 62 per cent, prothrombin time 25 seconds (normal 16), serum nonprotein nitrogen 30 mg. per cent (normal), and serum bilirubin 3.2 mg. per cent. Esophagram demonstrated varices.

The patient was admitted to the metabolism ward on Nov. 15, 1951, and continued on 45 Gm. daily of ion-exchange resins (Resodec) which had been started on the general ward service. A high-protein, medium-calorie diet, containing 10.4 meq. of sodium ion, was begun. Any excess of sodium noted in the balance resulted from that contained in the salt-poor albumin. A single paracentesis was performed on the fifty-second preoperative day, removing 1.3 L., for the patient's comfort. The incomplete periods noted during the fifty-six days of resin therapy resulted from the patient's refusal to save urine and stool specimens although the sensorium was clear. It may be seen in Fig. 4 that a negative sodium balance was achieved up to the first incomplete period in spite of the patient's failure to excrete this ion in the urine. There was a gradual decrease in the efficiency of the resins (Table X) with a corresponding failure to obtain a continued weight loss. A mild acidosis, with the lowest carbon-dioxide content recorded as 16 meq. per liter, probably resulted from the use of ammonium chloride, and it corrected itself without specific therapy in spite of the continued use of resin. No chemical hypokalemia was recorded.

While the over-all efficiency of the resins was not high (0.4 meq. of sodium ion per gram of resin), 612 meq. was removed which, in conjunction with a rigid low-sodium diet, was sufficient to stabilize and diminish the ascites in the presence of hypoalbuminemia.

On Jan. 15, 1952, 4 L. of ascitic fluid was found at operation when a portacaval shunt was performed. Postoperatively, the patient continued on a low-sodium diet (6 meq.) and developed no ascites. He died on the sixteenth postoperative day in hepatic coma, markedly jaundiced and with chemistry figures that were essentially normal (serum sodium 142, potassium 3.6, carbon dioxide 21, chloride 106 meq. per liter).

Fig. 4, *A*.


C.M. AGE: 52
MALE
DIAGNOSIS: CIRRHOSIS WITH ESOPHAGEAL VARICES AND ASCITES.
OPERATION: PORTACAVAL ANASTOMOSIS. 1-15-52.
INTAKE
BALANCE
OUTPUT
URINE
STOOL
WT.
SE. NA
NA BAL.
CO2
SE K
K BAL.
SE CL
CL BAL.
A/G
CAL.
PRE-OP DAYS
61 - 58 RESINS
A25 A25 A25
3 GM 3 GM 3 GM 3 GM
NH4CL
EXCHANGE RESINS 45 GM/DAY

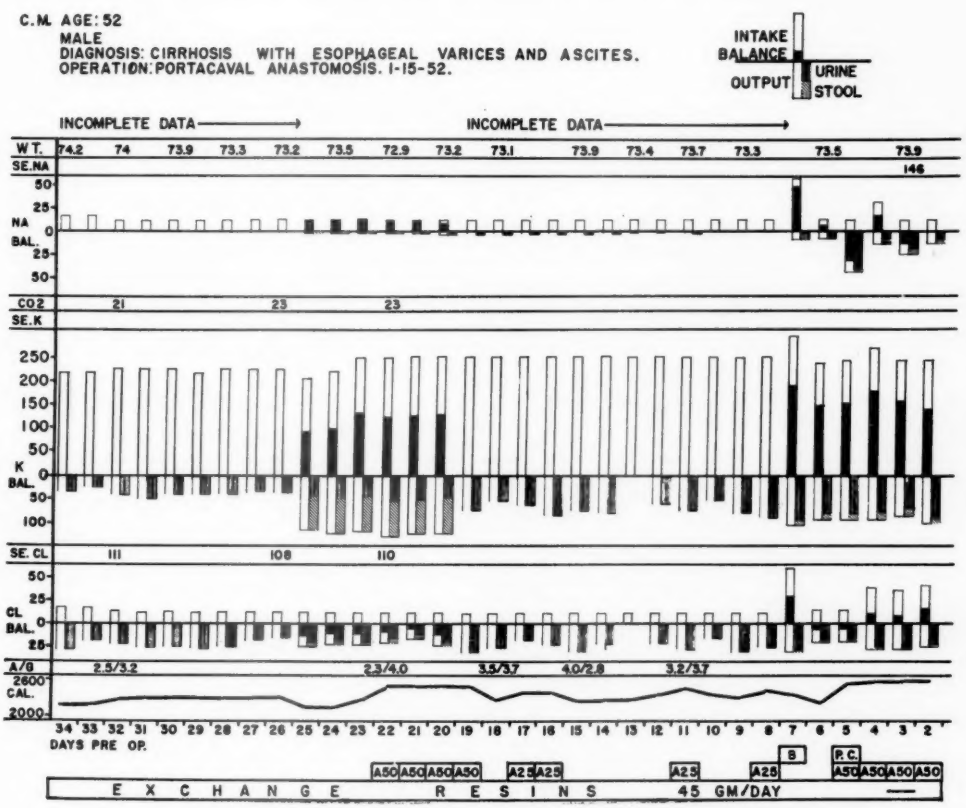

C.M. AGE: 52
MALE
DIAGNOSIS: CIRRHOSIS WITH ESOPHAGEAL VARICES AND ASCITES.
OPERATION: PORTACAVAL ANASTOMOSIS. 1-15-52.
INTAKE
BALANCE
OUTPUT
URINE
STOOL
INCOMPLETE DATA
INCOMPLETE DATA
WT.
SE. NA
NA BAL.
CO2
SE. K
K BAL.
SE. CL
CL BAL.
A/G
CAL.
DAYS PRE OP.
A50 A50 A50 A50
A25 A25
A25
A25
S
P.C.
A50 A50 A50 A50
EXCHANGE RESINS 45 GM/DAY

Fig. 4, *B*.

H. L. (Fig. 5, Table XI) was a 54-year-old woman with cirrhosis and ascites of three years' duration, both diagnoses being established at operation for removal of the gall bladder. She also had a thirty-six year history of duodenal ulcer. There were three episodes of hematemesis beginning in August, 1951. An abdominal exploration in February, 1952, again revealed cirrhosis of the liver with a large caudate lobe. Ascites and leg edema increased following this operation, making necessary a paracentesis in March, 1952. She was admitted to Presbyterian Hospital for the first time on March 22, 1952, and, because of vomiting brought on by pyloric obstruction secondary to a stenosing duodenal ulcer, a posterior gastroenterostomy was performed April 12, 1952, removing 4 L. of ascitic fluid at that time. The ascites reaccumulated quickly, requiring paracentesis following which the patient was transferred to the metabolism ward on May 1, 1952.

Examination revealed a thin, chronically ill woman with moderate ascites, a moderately enlarged liver and spleen, and 3 plus ankle edema.

Chemistry studies showed a total serum protein of 6.6 Gm. per cent, albumin 4.6 Gm. per cent, serum nonprotein nitrogen 49 mg. per cent (normal 25 to 30), Bromsulphalein retention 13 per cent after thirty minutes, serum bilirubin 0.9 mg. per cent, cephalin flocculation negative, prothrombin time 18.3 seconds (normal 15), serum carbon dioxide 18 meq. per liter.

The patient tolerated the diet poorly, eating only 1,400 calories and 55 Gm. of protein containing 9 meq. of sodium ion. On the twenty-sixth preoperative day 45 Gm. of Carbo-Resin was started and was taken daily.

It will be noted in Fig. 5 that the negative sodium balance created through stool loss without urinary excretion was of sufficient magnitude to stabilize and diminish the ascites. The mild acidosis reflected in the lowered carbon-dioxide content of the serum was not increased. As the stool output of potassium increased, chemically mild hypokalemia developed which corrected itself as the resins became less efficient, withdrawing a reduced amount of both sodium and potassium.

At operation on May 27, 1952, 4 L. of ascitic fluid was recovered and a splenectomy and splenorenal shunt were performed. Postoperatively, the total absence of urinary sodium led to a positive balance and the reaccumulation of ascites. The resins were given starting on the thirteenth postoperative day and proved quite efficient in extracting sodium. However, a paracentesis of 2.6 L. was required for comfort on the fifteenth postoperative day. Following this, the patient developed the clinical picture of hyponatremia (weakness, lethargy, and vomiting) and acidosis with a carbon-dioxide content of 14 meq. per liter. She received 2,000 c.c. of 5 per cent dextrose in saline solution with some improvement in the general feeling, but the acidosis increased in severity leading to the administration of 165 meq. of sodium lactate on both the twentieth and twenty-first postoperative days which corrected the clinical picture of acidosis. The resins were canceled on the twenty-fourth postoperative day.

At the time of discharge from the hospital on June 26, a mild degree of ascites appeared stable and the patient was given a diet containing 13 meq. of sodium.

Table XI shows the amount of sodium removed per gram of resin and the efficiency for each period.

It would appear that the patient's ability to tolerate sodium withdrawal had reached a critical point prior to entry into the metabolism ward. Following restricted intake of sodium and further withdrawal, she developed acidosis which was doubtlessly augmented by the release of acid radical from the resin, coupled with reduced renal function evident from a serum nonprotein nitrogen reading of 60 mg. per cent on the sixth postoperative day. The acidosis was not corrected with sodium chloride but was partly corrected with sodium lactate and completely corrected on the stopping of sodium withdrawal through the use of resins.

A follow-up from the local physician informed us that she died in August, 1952.

M. R. (Fig. 6, Table XII) was a 37-year-old woman, who gave a history of cirrhosis of three years' duration and ascites for the preceding seven months requiring paracen-

TABLE XI. QUANTITATIVE REMOVAL OF SODIUM AND POTASSIUM PER GRAM OF RESIN (PATIENT H. L.)

PERIOD	NUMBER OF DAYS	RESIN*		SODIUM†				POTASSIUM†			
		DAILY (GRAMS)	TOTAL (GRAMS)	INTAKE PER ORUM	OUTPUT (URINE)	OUTPUT (STOOL)	MEQ. PER GM. RES. IN STOOL	INTAKE PER ORUM	OUTPUT (URINE)	OUTPUT (STOOL)	MEQ. PER GM. RES. IN STOOL
26-13 days preoperative	14	45	630	8.1	0.6	19.0	0.4	170.1	15.8	73.4	1.6
12-8 days preoperative	5	45	225	10.3	3.3	12.2	0.3	203.4	17.7	175.7	3.9
7-1 days preoperative	7	45	315	10.4	3.6	2.2	0.05	200.1	24.5	16.3	0.4
1-12 days postoperative	12	0	0	24.0	2.0	0.8	0	33.9	22.9	7.9	0
13-23 days postoperative	11	44	480	7.1	0.9	26.2	0.6	94.5	14.4	49.6	1.1

Total amount of resin 1650 Gm.
Total stool sodium 631 meq. } 0.4 meq. sodium per gram resin

*Carbo-Resin, Eli Lilly & Company.
†Daily averages in total meq.

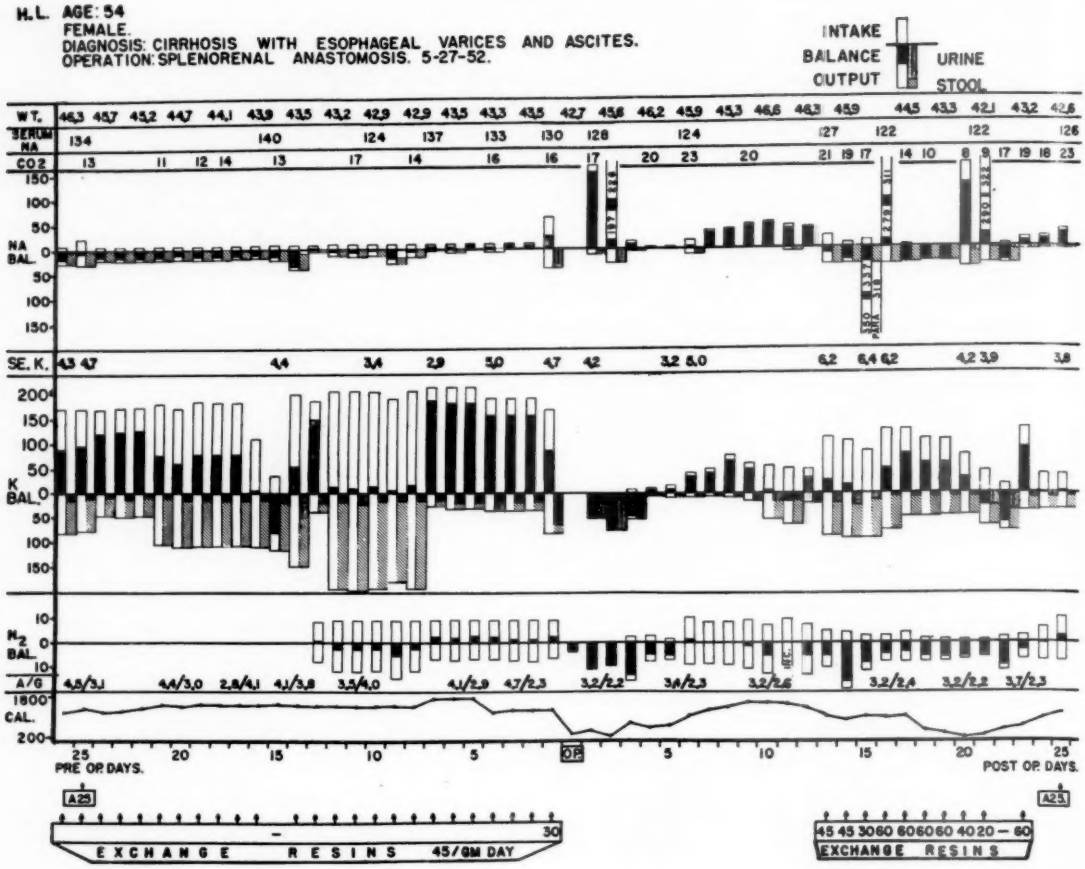
TABLE XII. QUANTITATIVE REMOVAL OF SODIUM AND POTASSIUM PER GRAM OF RESIN (PATIENT M. R.)

PERIOD (HOSPITAL DAYS)	NUMBER OF DAYS	RESIN*		SODIUM†				POTASSIUM†			
		DAILY (GRAMS)	TOTAL (GRAMS)	INTAKE PER ORUM	OUTPUT (URINE)	OUTPUT (STOOL)	MEQ. PER GM. RES. IN STOOL	INTAKE PER ORUM	OUTPUT (URINE)	OUTPUT (STOOL)	MEQ. PER GM. RES. IN STOOL
2-4	3	0	0	18.6	0	3.9	0	87.8	12.4	44.0	0
5-7	3	45	135	14.9	0	38.9	0.9	113.3	53.1	101.1	2.9
8-9	2	30	60	8.6	0.8	8.7	0.3	149.8	10.4	33.0	1.1
10-11	2	45	90	20.0	0	24.1	0.5	192.4	9.0	59.4	1.3
12-14	3	40	120	18.4	0	2.3	0.06	160.2	22.7	30.2	0.8
15-17	3	0	0	0	0.6	0	0	0	39.8	0	0

Total amount of resin 405 Gm.
Total stool sodium 189 meq. } 0.5 meq. sodium per gram of resin

*Carbo-Resin, Eli Lilly & Compnay.
†Daily averages in total meq.

Fig. 5.


H.L. AGE: 54
FEMALE.
DIAGNOSIS: CIRRHOSIS WITH ESOPHAGEAL VARICES AND ASCITES.
OPERATION: SPLENORENAL ANASTOMOSIS. 5-27-52.
INTAKE
BALANCE
OUTPUT
URINE
STOOL
WT.
SERUM NA
CO2
NA BAL.
SE. K.
K BAL.
N2 BAL.
A/G
CAL.
PRE OP. DAYS.
OP.
POST OP. DAYS.
EXCHANGE RESINS 45/GM DAY
EXCHANGE RESINS

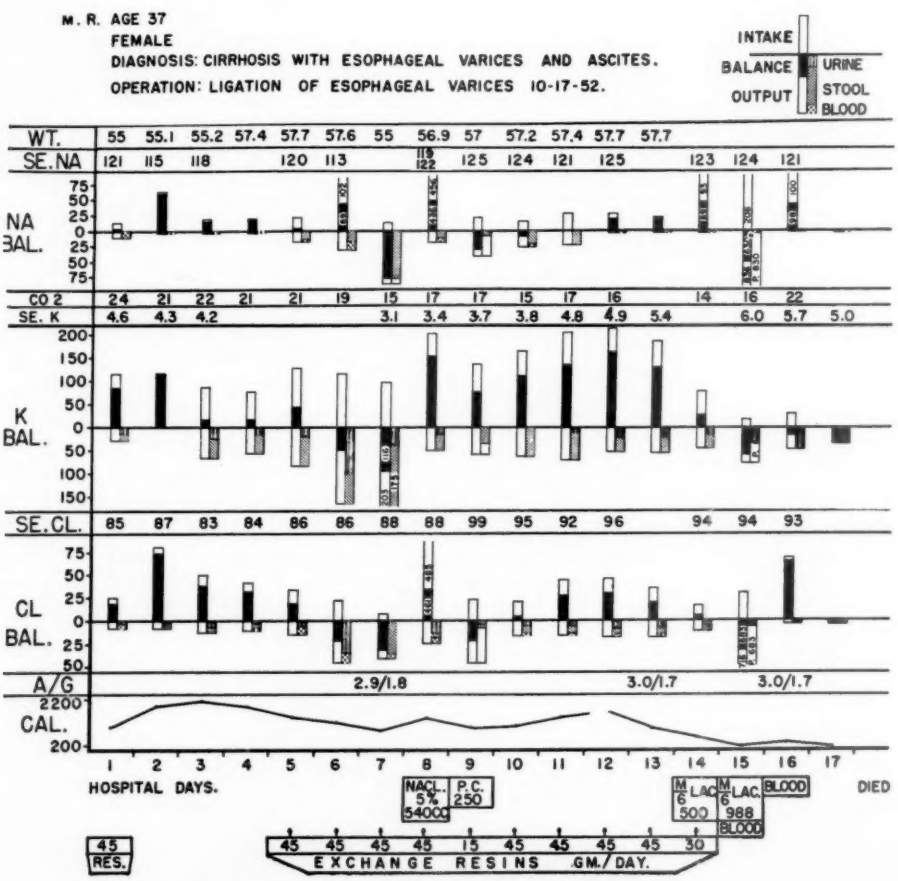

M. R. AGE 37
FEMALE
DIAGNOSIS: CIRRHOSIS WITH ESOPHAGEAL VARICES AND ASCITES.
OPERATION: LIGATION OF ESOPHAGEAL VARICES 10-17-52.
INTAKE
BALANCE
OUTPUT
URINE
STOOL
BLOOD
WT.
SE. NA
NA BAL.
CO2
SE. K
K BAL.
SE. CL.
CL BAL.
A/G
2.9/1.8
3.0/1.7
3.0/1.7
CAL.
HOSPITAL DAYS.
DIED
EXCHANGE RESINS GM./DAY.

Fig. 6.

tesis every seven to ten days. Several episodes of hematemesis occurred in the month prior to hospitalization and on admission Oct. 15, 1952, the patient was bleeding actively. A transesophageal ligation of varices was performed on Oct. 17 together with an abdominal paracentesis. She was transferred to the metabolism ward on Oct. 23.

Examination revealed marked ascites, 1 plus ankle edema, and a severe pharyngitis.

Chemistry studies showed a serum sodium of 121, potassium 4.6, carbon dioxide 24, and chloride 85 meq. per liter. The total serum protein was 4.5 Gm. per cent, albumin 3.1 Gm. per cent, Bromsulphalein retention 75 per cent after thirty minutes, prothrombin time 2.9 seconds (normal 15), cephalin flocculation 3+, serum bilirubin 5.6 mg. per cent, blood urea nitrogen 39 mg. per cent (normal 15).

The patient was placed on balance studies on admission and tolerated only a low- to moderate-calorie diet containing 11 to 20 meq. of sodium. On the first day, she received 45 Gm. of Carbo-Resin by error and was then started on resins on the fifth day. During the three-day control period 0 to 2 meq. of sodium was recovered from the urine per day. On the eighth day of study, because of the clinical picture of hyponatremia, she was given 443 meq. of sodium as sodium chloride which resulted in slight clinical improvement, little change in serum sodium, and a 2.5 L. increase in the volume of ascites (direct measurement by dye dilution). On the fourteenth day of study, a slowly developing acidosis became clinically obvious and she received 83 meq. of sodium ion as sodium lactate. An additional 165 meq. was given the following day when the resins had been stopped. A paracentesis was performed on this same day removing 6.8 L., and a severe anemia was corrected in part with 1,000 c.c. of whole blood.

Because of the beginning of development of chemical hypokalemia, as noted by the serum level of 3.1 meq. per liter on the seventh day, she was given 60 meq. of potassium as salt daily by mouth, resulting in a positive balance and a return of the serum-potassium level to normal.

Table XII depicts the efficiency of the resins in removing sodium via the stool.

A severe pharyngitis, which was noted following the operation for ligation of the varices, developed into a pseudomembranous laryngitis requiring repeated removal of the membrane by direct laryngoscopy. A tracheotomy became mandatory on the sixteenth day of study, and the patient died on the eighteenth day in coma.

It is apparent that this patient was both acutely and chronically ill. The use of an intratracheal tube at operation for anesthesia led to an uncontrollable pharyngitis and laryngitis which culminated in death. The clinical picture of hyponatremia which was treated with hypertonic saline solution intravenously, resulted primarily in an increase of ascitic fluid. The acidosis resulting from diminished renal function, sodium withdrawal, and release of acid radical from the resins was corrected through the administration of sodium lactate and discontinuance of the resin.

DISCUSSION

While the several mechanisms involved in the process leading to the formation of ascites are not entirely clear, it is apparent that the primary factor is the renal retention of sodium, secondary to increased tubular reabsorption. The more sodium ingested and retained, the faster the accumulation of ascites. Portal hypertension and hypoalbuminemia play a variable and usually secondary role.

It has been documented that a low to rigidly low (20 to 10 meq.) sodium intake will control the formation of ascites, but reabsorption requires months. Reabsorption can only occur in association with a negative sodium balance, which is not seen in patients with marked ascites. Ascites is not controlled by

repeated paracentesis since the forces at play are sufficiently strong to produce reaccumulation resulting, in some instances, in chemical and clinical hyponatremia. This "low salt syndrome"[23, 52-55] has been well described and was encountered in Patients M. R. and H. L. Patients differ in ability to tolerate withdrawal of sodium based on the degree of liver damage, diminished renal function, response to acidification, and possibly total body sodium at the outset of treatment.

The effect of mercurials, augmented by ammonium chloride, in producing sodium diuresis where maximal ascites formation is recurring is negligible.

A positive sodium balance on a rigid low-sodium diet may be changed to a negative one by the use of ion-exchange resins. The expected efficiency of the resin is about 1 meq. of sodium ion per gram of resin when the dietary intake of sodium is moderate (30 meq.). This figure is not usually approached on a low sodium intake, as may be seen in the tables of the five patients cited. In addition, the efficiency decreases with continued use. Resins may not be used without possible complications the most common of which is acidosis. This is apparently brought about by the absorption of acid radicals from the resin and the removal of the main alkaline-buffering ion sodium. Decreased renal and hepatic function, leading to diminished excretion of titratable acid and failure of conversion of ammonia to urea, respectively, augment this tendency to acidosis. The severe toxic reactions encountered by Gabuzda and associates[50] were not seen in our patients.

The suggestion[45, 49] has been made that a moderate dietary intake of sodium, combined with the use of resin, might lead to a more palatable diet and a negative sodium balance. While this is so in theory, it cannot be relied upon in practice because of the unpredictable efficiency of the resins. Patient L. B. is a case in point where even a rigidly low sodium intake combined with the use of resin resulted in a positive balance. While it may be argued that the resins would be more efficient if more sodium were available in the diet, a positive sodium balance in this patient could almost be predicted with certainty.

The time factor for reabsorption of ascites becomes important in the management of those patients who have repeated hemorrhage from esophageal varices. Those patients with marked liver damage and severe ascites who are bleeding from varices are not candidates for immediate portacaval shunt. The bleeding might be better controlled through the use of esophageal balloon tamponade or transesophageal ligation of varices. Some of the very sick patients are certainly unable to tolerate a negative sodium balance and operation. It is necessary to be content with stabilization of ascites through the use of a low sodium intake until such time as liver function improves. When liver function improves, after many months of vigorous therapy and control, a spontaneous diuresis and loss of ascites may be noted or a negative sodium balance may be produced through the use of resins. Only at such time should a major operative procedure such as portacaval shunt be considered. This would apply to Patients C. M. and H. L.

Prior to operation, any hypoalbuminemia should be corrected with the intravenous administration of salt-poor albumin so as to restore normal os-

motic relationships. Following operation, a low-sodium diet should be given until such time as the patient demonstrates the ability to excrete sodium in the urine in sufficient amounts to indicate the re-establishment of normal balance, thus preventing the accumulation of ascites.

CONCLUSIONS

1. A low-to-rigidly-low (20 to 10 meq.) sodium content in a high-protein and calorie diet is required to prevent the formation of ascites.

2. Reabsorption of ascites will occur with a negative sodium balance which may be accomplished with the aid of ion-exchange resins in selected patients.

3. The use of resins in these patients is not without danger and should be given only on an in-hospital basis.

4. Patients with cirrhosis, ascites, and bleeding from esophageal varices should have the bleeding controlled with an esophageal balloon or transesophageal ligation of varices. Immediate decompression of portal pressure should not be attempted.

5. After liver function improves and ascites has been stabilized or reabsorbed, the portacaval shunt operation may be undertaken when indicated.

6. It is recommended that a low-sodium diet be employed following operation until such time as the patient demonstrates the ability to excrete sufficient sodium in the urine to achieve normal balance.

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DISCUSSION ON "EXPERIENCES WITH PORTACAVAL ANASTOMOSIS IN THE TREATMENT OF PORTAL HYPERTENSION" BY DR. CHARLES B. RIPSTEIN,* AND "THE MANAGEMENT OF CIRRHOSIS OF THE LIVER AND ASCITES WITH PARTICULAR REFERENCE TO THE PORTACAVAL SHUNT OPERATION" BY DR. DAVID V. HENRY T. RANDALL, AND DR. HARRY S. SOROFF

DISCUSSION

DR. JOHN T. REYNOLDS (Chicago, Ill.).—I have only one comment, and that concerns the question of the interpretation of portal pressures which are taken in the operating room. As some of you may know, Dr. Julian last year, at the meeting of the American College of Surgeons, mentioned patients he had seen in whom the portal pressure as determined at the time of operation was the same as that in the vena cava, the implication being that portacaval anastomosis would not result in decompression of the portal system. I have recently operated upon a patient who had had massive esophageal bleeding. The pressure in the splenic vein was 220 mm. of water at the time of operation, and the pressure in the renal vein was 105 mm. of water. A large satisfactory anastomosis was carried out, and at the conclusion of the operation the pressure in the splenic vein was 285 mm. of water. However, through the thin-walled veins, it was possible to see the vigorous surge of blood from the splenic vein into the renal vein. The rise in pressure in the splenic vein after a very satisfactory anastomosis (vigorous side-circuiting into the caval system) can only emphasize the fact that our preoperative reading of the splenic vein pressure did not represent the actual condition of portal pressure, but rather represented

*See page 570 for article by Dr. Ripstein.

a condition which had been influenced by the trauma and the blood loss incident to dissecting the splenic vein. Had the pressure in such a case been a little lower, and had the pressure in the vena cava been a little higher, it might well have been conceivable that this man would have been considered unsuitable for anastomosis, an interpretation which was not justified.

DR. WILLIAM D. HOLDEN (Cleveland, Ohio).—I would like to discuss some observations that Dr. Cole, Dr. Cline, and I have made at University Hospitals of Cleveland. They may be extended by many of you and they may possibly have some bearing on the production of ascites which was alluded to by Dr. Habif. He mentioned the four possible factors that are concerned with the production of ascites in those patients who have intrahepatic disease: the portal pressure, the osmotic pressure, the tendency to sodium retention, and the hormonal control of fluid balance. Our observations concern the hormonal control of fluid balance and this work will shortly be published in *Surg., Gynec. & Obst.* What we have been able to do is to demonstrate a marked increase in the antidiuretic principles that can be extracted from the urine of patients who are operated upon, and we have observed that there is a rough correlation between the extent of surgical stress and the amount of antidiuretic principle that can be recovered in the urine.

Other people have made observations, too, to the effect that there is an increase in the amount of antidiuretic principle that can be recovered in patients who have a serious depression of liver function, and presumably the liver has a great deal to do with maintaining a normal balance between the antidiuretic principles and the diuretic principles, whatever they may be.

This is an extremely difficult field, and the whole question is still confusing. Little is understood about the antidiuretic factors. I do not wish to leave the impression that this is the most important factor in the production of ascites, but it is a possible one and many more observations are needed to evaluate the role of the various factors which Dr. Habif mentioned before we will be able to understand the formation of ascites. I think a great deal of useful information can be obtained by someone studying the hormonal control of water balance, especially in patients who have serious liver disease.

STUDIES OF COMBINED VASCULAR AND NEUROLOGICAL INJURIES

II. The Effect of Arterial Ligation and of Sympathetic Denervation Upon Return of Function After Crushing the Sciatic Nerve of the Rat

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THE difficulties encountered in the management of combined vascular and neurological injuries and the dearth of knowledge concerning the precise interrelationship of somatic and sympathetic activity and paralysis upon the circulatory and nutritional status of the extremity and of the adequacy of blood flow upon neural repair have prompted us to undertake certain experimental studies directed toward the clarification of these and related problems. Our initial efforts were concerned with the effect of somatic and sympathetic denervation upon the results of arterial ligation in the rat.[1] It was found that the simultaneous ligation of the common iliac and common femoral arteries of an extremity was followed by a low incidence of tissue necrosis but a very high incidence of ischemic paralysis. Immediate sympathectomy was effective in hastening recovery from this ischemic paralysis. When such arterial ligation was combined with section of the sciatic nerve, recovery of neural function was markedly delayed and the occurrence of tissue necrosis was strikingly increased. Sympathectomy brought about a great reduction in the frequency of necrosis of tissue. In these experiments the fibers of the sciatic nerve were sectioned completely with preservation of the neural sheath. Recovery of neurological function was slow. During periods of observation as long as one year it was not complete in any animal subjected to arterial ligation as well as sciatic section. The present study was designed to inquire into the effect of arterial ligation and of sympathetic function and paralysis upon recovery of function after crushing the sciatic nerve.

MATERIALS AND METHODS

Domestic albino rats weighing from 160 to 230 grams were used. The animals were anesthetized by the intraperitoneal administration of Sodium Amytal, .033 Gm. per kilogram of body weight. The operations were performed with clean but not aseptic technique. The neurological injury was inflicted by crushing for 10 seconds the left sciatic nerve with an especially fashioned clamp, the jaws of which were polished and cut to a width of 1 mm. The nerve was exposed in the buttock by splitting the fibers of the gluteus muscle and was crushed in all animals at the same level. The arterial injury consisted of division between fine silk ligatures of the left common iliac and left common femoral arteries. The former were divided transperitoneally. Sympathectomy

[1] Read at the meeting of the Society of University Surgeons, St. Louis, Mo., Feb. 12-14, 1953.

was also performed transperitoneally. The chain was resected under a dissecting microscope from the level of the renal vessels to the bifurcation of the aorta.

In the first group of animals the sciatic nerve was crushed. In the second group the arteries were divided and the nerve was crushed at one sitting. In the third group a sympathectomy and iliac arterial division were performed on one day, and on the following day the nerve was crushed and the femoral artery divided. In the fourth group sympathectomy and crushing of the sciatic nerve were carried out at the same time. The final group of animals was subjected to crushing of the sciatic nerve followed 10 days later by lumbar sympathectomy.

A solution of dilute picric acid was applied to the extremity immediately after crushing the sciatic nerve and twice weekly until recovery of nerve function was complete. This measure was effective in preventing the animals from gnawing upon the anesthetic limb. The animals were kept in cages in a room maintained constantly at 72° F. and were fed a standard laboratory diet. Each was observed daily, and return of neurological function was judged to have taken place completely as soon as normal fanning of the toes was demonstrable.

OBSERVATIONS

Sciatic Crush.—The control group consisted of 31 animals subjected to crushing of the sciatic nerve. Recovery of nerve function took place in from 21 to 59 days. In 22 of the animals the period of regeneration ranged from 32 to 40 days. The mean was 35 and the median was 36 days. Necrosis of toes was observed in 9 animals or 29 per cent. Altogether, tissue necrosis occurred in 22 digits, or 14 per cent of the total number of toes on the affected extremities.

Sciatic Crush and Arterial Ligation.—In 20 rats crushing of the sciatic nerve was combined with arterial ligation. The interval before return of complete nerve function was considerably longer than in the first group. Sixteen of the animals had return of function in from 29 to 108 days, while 4 animals were still completely paralyzed 108 days after nerve crushing. For purposes of statistical analysis the latter 4 animals were handled as if they had return of function in 108 days, a method of treatment which tends, of course, to minimize the prolongation of the period of regeneration. Under these circumstances the mean is calculated to be 54.5 days, the median 38.5. Necrosis of tissue was noted in 6 animals or 30 per cent. Altogether 20 toes were so affected, 20 per cent of the total number of toes.

Sciatic Crush, Arterial Ligation, and Sympathectomy.—Eighteen animals were subjected to crushing of the sciatic nerve, arterial ligation, and sympathectomy. The interval before return of full nerve function was shorter than in the group with sciatic crush alone, the mean being 25.9 days, the median 25. The interval varied from 23 to 43 days. With the exception of 1 animal, it ranged between 23 and 28 days and with the exception of 2 animals, between

23 and 26 days. Necrosis of digits was noted in only 2 animals (11 per cent) and involved only 6 toes, or 6.6 per cent of the total number of toes.

Sciatic Crush and Sympathectomy.—In 18 animals the sciatic nerve was crushed and sympathectomy performed. The interval before return of full nerve function was still shorter, the mean being 20.4 and the median 20 days. The period ranged from 18 to 24 days. Necrosis of digits was observed in only 2 animals (11 per cent) and involved only 4 digits or 4.4 per cent of the total.

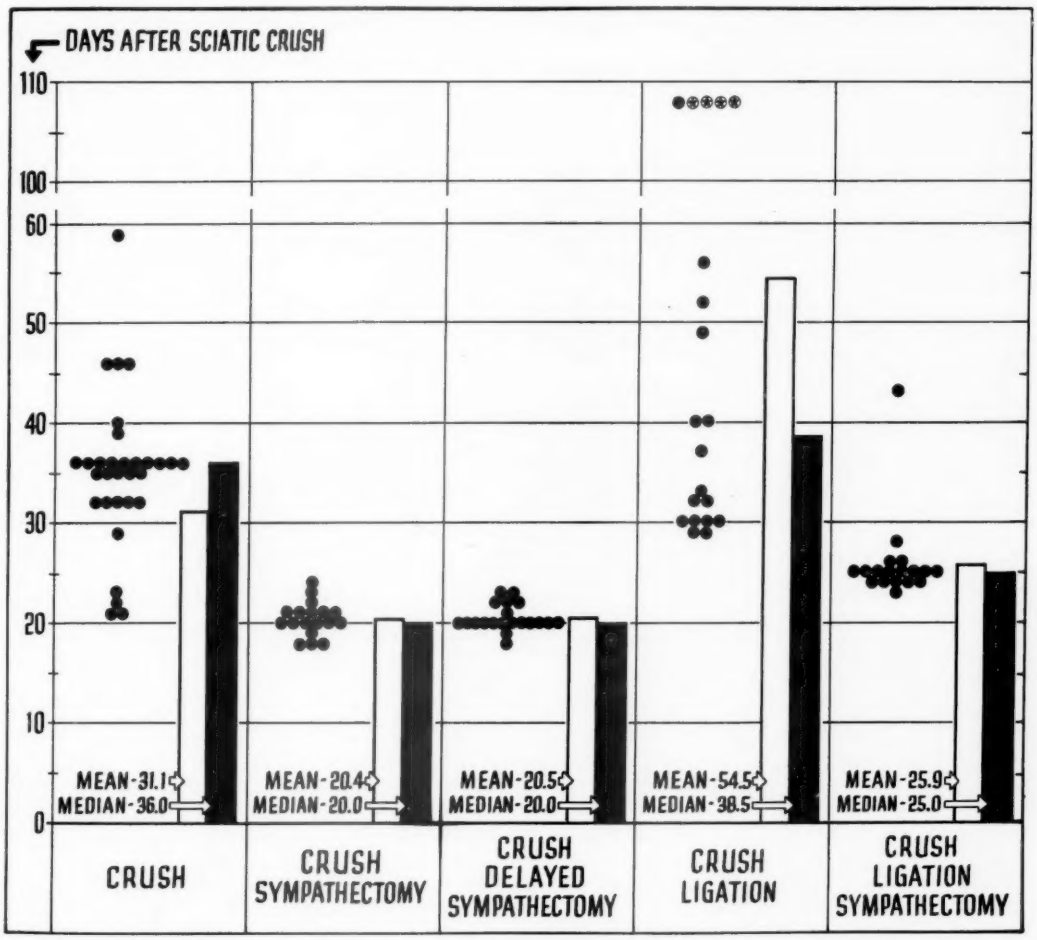

Fig. 1.—Chart showing distribution of time interval between sciatic nerve crushing and return of normal neurological function, with mean and median values, in the 5 groups of animals.

Sciatic Crush Followed Ten Days Later by Sympathectomy.—In 20 animals crushing of the sciatic nerve was followed 10 days later by lumbar sympathectomy. The results were comparable to those of the preceding group. The period before return of complete nerve function varied from 18 to 23 days, the mean being 20.5 and the median 20 days. Necrosis was observed in only a single digit.

The results in the 5 groups of animals are compared in Fig. 1 and in Tables I and II. It is apparent that arterial division prolonged the interval

before return of nerve function and that sympathectomy shortened the period appreciably, whether performed just before, or 10 days after, sciatic crushing and even in the presence of divided main-stem arteries, The results have been analyzed statistically by determining the "t" ratio. Obviously there was no difference between the last 2 groups, the period of regeneration being precisely the same whether sympathectomy was performed simultaneously with, or 10 days later than, the crushing of the sciatic nerve. The differences between any one of the other 4 groups and all the others are highly significant, the ratios varying from 3.19 to 8.41 and all but 1 being 3.68 or greater. It is equally apparent that there was a trend toward a decreased incidence of tissue necrosis when sympathectomy was performed. This was true even when there was concomitant arterial ligation. When analyzed statistically by the chi square method, the percentage of toes affected was significantly less in the three groups treated by sympathectomy as compared with the control animals and highly significant as compared with those subjected to crushing of the sciatic nerve and division of the arteries. There is no statistical significance to the apparent slight increase in the percentage with necrosis in those animals in which arteries were divided in addition to crushing the sciatic nerve as compared with the controls.

DISCUSSION

These studies demonstrate that the rate of regeneration of the crushed sciatic nerve as measured by return of full neurological function is dependent

TABLE I. COMPARISON OF RATE OF RETURN OF NERVE FUNCTION AFTER CRUSHING THE SCIATIC NERVE AND WITH CONCOMITANT ARTERIAL INJURY, OR SYMPATHECTOMY, OR BOTH

INTERVAL IN DAYS BEFORE RETURN OF FUNCTION	SCIATIC CRUSH	SCIATIC CRUSH AND ARTERIAL LIGATION	SCIATIC CRUSH, ARTERIAL LIGATION, AND SYMPATHECTOMY	SCIATIC CRUSH AND SYMPATHECTOMY	SCIATIC CRUSH AND DELAYED SYMPATHECTOMY
Range	21 to 59	29 to 108 +	23 to 43	18 to 24	18 to 23
Mean	35.1	54.5 +	25.9	20.4	20.5
Median	36.0	38.5 +	25.0	20.0	20.0

TABLE II. COMPARISON OF INCIDENCE OF TISSUE NECROSIS AFTER CRUSHING THE SCIATIC NERVE AND WITH CONCOMITANT ARTERIAL INJURY, OR SYMPATHECTOMY, OR BOTH

TYPE OF INJURY OR TREATMENT	TOTAL NUMBER OF ANIMALS	ANIMALS WITH TISSUE NECROSIS		TOES WITH TISSUE NECROSIS	
		NUMBER	PER CENT	NUMBER	PER CENT
Sciatic crush	31	9	29.0	22	14.1
Sciatic crush and arterial ligation	20	6	30.0	20	20.0
Sciatic crush, arterial ligation, and sympathectomy	18	2	11.0	6	6.6
Sciatic crush and sympathectomy	18	2	11.0	4	4.4
Sciatic crush and delayed sympathectomy	20	1	5.0	1	1.0

upon the blood supply to the limb. When the common iliac and the common femoral arteries were divided, the interval before return of complete nerve function was significantly prolonged. The interval was appreciably shortened when sympathectomy was performed either at the same time the sciatic nerve was crushed or 10 days later.

It was a surprising observation that the period of regeneration was appreciably shortened in sympathectomized animals as compared with the control group in which the arterial supply was intact and in which one would have imagined that blood flow was perfectly adequate. This observation could be explained in several ways. In the first place, one might assume that the "cold phase," which in human beings with somatic nerve paralysis follows the initial "warm phase," occurs early in the rat during the period of regeneration and is eliminated by sympathetic denervation. Against such an assumption is the fact that there was no evidence from carefully performed skin temperature measurements in rats exposed to a constant environment that these animals underwent a "cold phase" during the period of observation. Indeed, under such circumstances, the skin temperature of the paralyzed extremity remained essentially the same as that of the contralateral normal extremity. The details of these observations will be reported separately in a study concerned with the response during exposure to a cool atmospheric environment of various species of animals subjected to sympathetic denervation, somatic nerve paralysis, or both. In the second place, one might suppose that the blood flow was normal in the limbs of the control group which was subjected only to crushing of the sciatic nerve and that the speedier return of neural function in those animals treated by sympathectomy is to be explained by a superabundance of circulation in the limb. In the third place, one could entertain the hypothesis that actual vasoconstriction might be present in the proximal portion of the extremity in spite of the sympathetic paralysis in the anesthetic portion of the limb which follows crushing of the sciatic nerve. In that case the enhanced return of neural function in those animals treated by sympathectomy could be explained by the substitution of vasodilatation for vasoconstriction in the nonanesthetic portion of the limb. That the latter consideration may be valid is suggested further by the fact that, remarkably enough, return of function was actually quicker in those animals subjected to crushing of the sciatic nerve, arterial division, and sympathectomy than in those in which the sciatic nerve was simply crushed. Additional investigations are being planned which may throw light upon this problem. It was a puzzling observation that the period of regeneration was just as short in those animals in which sympathectomy was performed 10 days after crushing the sciatic nerve as in those animals in which it was carried out simultaneously with the crushing.

The reported studies are at variance with the conclusions drawn by Baesich and Wyburn[2] who crushed both sciatic nerves of rabbits and on one side mobilized the nerve extensively and divided all collateral nutrient arteries in the gluteal, femoral, and saphenous groups. Microscopically they found no difference in the rate of growth of the nerve in the two limbs. They con-

cluded, therefore, that regenerating nerves are not influenced by interference of blood supply, a conclusion difficult to reconcile not only with our experimental observations but with the obvious retardation of neural repair in human cases of combined neurological and vascular lesions.

The current experiments confirm the previously reported findings concerning the value of sympathetic denervation in affording protection from the tissue necrosis which sometimes follows somatic nerve injury, and which in earlier studies[1] more commonly followed somatic nerve injury combined with arterial interruption.

These studies should prove of value in the management of patients. Because there is sympathetic paralysis in the area of anesthesia and because the extremity goes through a warm phase characterized by vasodilatation in the anesthetic portion of the limb shortly after complete division of a peripheral nerve, it has commonly been felt that sympathectomy is useless in such conditions. We are persuaded that this attitude may be based upon erroneous considerations. The occurrence of sympathetic paralysis in the anesthetic skin does not necessarily indicate that blood flow is maximal in other portions of the limb nor that the injured nerve itself is receiving adequate circulation. It has previously been reported[3] that a marked increase in oscillometric readings may be observed after sympathectomy in extremities in which the surface temperature had been previously high and stable as a result of somatic anesthesia. Furthermore, experiences with sympathectomy in cases of combined neurological and vascular injury obtained by one of us (H. B. S.) have given him the impression that this procedure is of value in enhancing the return of proper nerve function. It is admittedly difficult to control adequately such observations in patients because of the variability in neural damage and impairment of circulation from one patient to another. The present animal studies certainly suggest that the adequacy of circulation is of utmost importance in the return of nerve function. The enhancement of somatic neural regeneration in animals with intact arteries when subjected to sympathectomy is an interesting and rather surprising finding. It would be most valuable if controlled observations of this sort could be made in human subjects.

CONCLUSIONS

1. The return of nerve function in the rat is influenced greatly by the circulatory status of the limb.

2. Division of main arterial stems to the extremity significantly prolongs the interval before return of nerve function after crushing the sciatic nerve.

3. Sympathetic denervation significantly shortens the period before return of neural function of the paralyzed sciatic nerve. This is the case whether sympathectomy is performed at the time of crushing the nerve or 10 days afterward. It is also the case in animals subjected to division of main arterial stems in addition to crushing the sciatic nerve.

4. Sympathectomy decreases the incidence of tissue necrosis following crushing of the sciatic nerve.

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THE AFTERMATH OF PERFORATED DUODENAL ULCER

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RECENT reports on the follow-up of perforated duodenal ulcers treated by simple closure which are at variance with previously accepted conclusions provided the stimulus for this study.

The literature until recently is abundantly optimistic about the good results attained by simple closure. In 1931, White and Patterson[1] in an excellent review of the literature and on the basis of their own experience concluded that of every 100 patients that leave the hospital following simple closure of an acute perforation, approximately 60 to 65 will remain free of gastric symptoms, approximately 10 to 15 will require further surgery, and, of the remaining 25, those who are reasonably careful about diet and general activity will get along satisfactorily.

Twenty years later in 1951, Turner,[2] reporting on 147 patients observed for twenty years following closure of a perforation, stated that more than 85 per cent of these patients continued to have ulcer symptoms which were quite severe in three-fourths of the cases. Over one-third of the patients required additional surgery. Only one-seventh remained symptom free. Also in 1951, Tovee,[3] reporting on 78 patients followed from five to twenty years after simple closure, found that one-third had little or no trouble with their digestive apparatus subsequently; one-third had typical or severe symptoms of ulcer characterized by pain, nausea and vomiting, or bleeding episodes, and one-third had undergone further operative procedures consisting of gastrectomy, gastroenterostomy, or closure of another perforation.

This high incidence of complications following simple closure has resulted in a definite swing toward more radical surgery at the time of perforation. Ever since Von Haberer in 1919 performed immediate gastrectomy for acute perforation, an increasing number of supporters have expressed similar convictions.[4-8] A middle-of-the-road attitude has also been advanced, and recently Dodson[9] had advocated delayed primary gastrectomy within four weeks from the time of closure.

In the light of these reports, a review of the perforated duodenal ulcers treated at the Genesee and Strong Memorial Hospitals was undertaken to determine their aftermath. This review comprises 101 patients admitted to the Genesee Hospital from 1933 through 1950 and 148 patients admitted to the Strong Memorial Hospital from 1926 through 1950. Of this total of 249 patients there were 231 men or 92.7 per cent and 18 women or 7.3 per cent, with a ratio of 13 to 1. There were 8 perforations in the Negro, or 3.3 per cent of all cases, which is about a normal ratio for the population in this area and is in accord

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with the findings of Odon and De Bakey[10] as well as Garver.[11] There were no perforations before the age of 10 years, the youngest patient being 17 and the oldest 83 years of age.

Table I shows the relative breakdown in decades. The majority or 181 cases out of 249 representing 72.9 per cent occurred between the ages of 30 and 60 years.

TABLE I. INCIDENCE OF PERFORATED DUODENAL ULCERS

AGE (YEARS)	NUMBER OF CASES	PER CENT
10 to 20	4	1.6
21 to 30	29	11.6
31 to 40	51	20.7
41 to 50	65	26.1
51 to 60	65	26.1
61 to 70	21	8.3
71 to 80	13	5.3
81 to 90	1	0.3
Total	249	100.0

In 20 cases, or 8 per cent of the total, no history of ulcer symptoms could be obtained, and in 178 cases, or 71 per cent, the ulcer history was less than one year's duration.

Much has been written about the duration of the perforation and its effect on the mortality rate. A review of the above-mentioned cases supports the prevailing contentions, but it must be stated that the accuracy of the onset of the perforation in many instances is an assumption only. In many of the cases the history suggested a temporary walling off of the perforation for several days to several weeks followed by an acute exacerbation with sudden collapse. In the light of these findings no attempt was made to pinpoint the exact time of perforation.

Of the 249 cases, 128 or 51.4 per cent had roentgenograms taken for free air with positive findings in 93 of the cases studied, representing 72.6 per cent. From the records of both hospitals it appears that routine films were not the standard procedure until 1945. In an attempt to demonstrate free air beneath the diaphragm it is important that films be taken in the left lateral position as well as the upright. In reviewing this series the presence of free air was more constantly noted in the left lateral position which is in accord with the findings of Williams and Hartzell.[12]

There were 12 patients treated conservatively with 1 survival. The diagnosis in all these cases was confirmed either by the presence of free air beneath the diaphragm or by post-mortem examination. The one survivor returned two years following perforation with signs of pyloric obstruction, and a gastric resection was performed. This series treated by conservative measures represents a group that was too bad a risk for surgery and it is doubtful that surgery would have benefited any of the 11 who died. All of these patients had been perforated for more than twenty-four hours and presented serious coexisting cardiorenal vascular disease. De Bakey[13] is of the opinion that the minimum standard for conservative treatment is a perforation of at least twelve hours'

standing, and Taylor[14] advises surgery only in those patients in whom there is a history of food ingestion in the period immediately antedating the perforation.

Of the 249 patients treated, 237 or 95.2 per cent were subjected to surgery. Of these, 142 or 59.8 per cent were on the staff service and 95 or 40.2 per cent on the private service. There were 54 different surgeons on the resident staff and 27 different surgeons on the private service responsible for the operative procedures instituted. There were 30 deaths attributed to surgery for an overall mortality rate of 12.7 per cent. Of the 30 deaths, 24 were on the staff service and 6 occurred on the private service (Table II).

TABLE II.

	NUMBER OF CASES OPERATIVE	PER CENT	MORTALITY	PER CENT
Staff	142	59.8	24	16.9
Private	95	40.2	6	6.3
Total	237	100.0	30	12.7

In 7 of the 30 deaths an additional procedure to simple closure of the perforation had been undertaken. Associated with pyloroplasty there were 3 deaths, with posterior gastroenterostomy 3 deaths, and 1 death with an appendectomy. Post-mortem findings in the latter case revealed a generalized peritonitis secondary to a perforation of the cecum. In the early years, in addition to simple closure, there were 10 pyloroplasties, 11 posterior gastroenterostomies, and 8 appendectomies performed. No gastric resections were performed at the time of simple closure. Of the 10 pyloroplasties, 6 were of the Heineke-Mikulicz type, 3 of the Finney type, and 1 was a Judd pyloroplasty. Of those undergoing Heineke-Mikulicz operations, 3 patients died following surgery, 1 developed pyloric obstruction five years later requiring definitive surgery, and 2 remained asymptomatic. All 3 patients with a Finney pyloroplasty developed severe bleeding later on, and in each instance a gastric resection was performed. There developed in the 1 patient with a Judd pyloroplasty a pyloric obstruction nineteen years later. Of the 11 patients with gastroenterostomies, 3 died following surgery, 2 developed bleeding marginal ulcers, and 6 were asymptomatic. Of the 8 patients with associated appendectomy 1 died following surgery.

Immediate Complications.—No attempt was made to analyze all the complications that developed. Immediate complications in this instance refer directly to the operative procedure during the initial hospitalization, of which there were 9. Pyloric obstruction developed in 5 patients, requiring a gastroenterostomy in each case. Severe bleeding developed in 4 cases and 1 of these required a gastric resection thirteen days later. Another one had a Finney pyloroplasty performed twenty-one days later. This latter patient returned two years later with an active ulcer but responded to medical therapy. The remaining 2 patients were treated medically. One returned sixteen months later with hemorrhage for which a gastric resection was performed. The other one remained asymptomatic.

Aftermath.—A satisfactory aftermath was obtained in 167 of these patients. Of the 167 cases followed, 109 or 65.1 per cent developed major sequelae (Table III).

TABLE III. MAJOR SEQUELAE

	NUMBER OF CASES	PER CENT OF TOTAL	LESS THAN SIX MONTHS	PER CENT	THREE YEARS	PER CENT	OVER THREE YEARS	PER CENT
Reperforations	15	8.9	2	13.3	8	53.3	5	33.4
Active ulcer	14	8.4	4	28.5	7	50.0	3	21.5
Pyloric obstruction	57	34.2	19	33.3	23	40.9	15	25.8
Hemorrhage	23	13.8	5	21.7	10	43.5	8	34.8
Asymptomatic condition	58	34.7						
Total	167	100.0	30	100.0	48	100.0	31	100.0

Of the 15 cases of reperforation, in 1 instance it followed a posterior gastroenterostomy performed twenty years earlier at the time of simple closure. The time interval of reperforation was as follows: 2 patients reperforated in less than six months, 1 in eighteen months, 4 in two years, 3 in three years, 3 in six years, 1 in twelve years, and 1 in twenty years.

In the 14 cases of active ulcer the symptoms had recurred in 4 within six months, in 7 within three years, and in 3 after three years.

In the 57 cases of pyloric obstruction, the diagnosis was made in 19 cases within six months, in 23 within three years, and in 15 after three years.

In the 23 cases of hemorrhage, the symptoms appeared in 5 patients within six months, in 10 within three years, and in 8 after three years.

There were 58 patients who could be considered asymptomatic. Of the 167 patients followed, 61 or 36.5 per cent required further surgery.

A simple closure was performed in the 15 cases of reperforation. None of the 14 patients with active ulcer were operated on.

In the group of 57 patients with pyloric obstruction, 34 were operated upon; and of the 23 patients with hemorrhage, 12 required subsequent surgery.

DISCUSSION

It is important to remember that a perforation of a duodenal ulcer can occur in the absence of an ulcer history. In the review of the records the absence of an ulcer history accounted for the failure of preoperative films in a number of instances. Errors in preoperative diagnoses were likewise a factor in this respect. It is reasonable to expect that a number of these patients would have shown free air in the peritoneal cavity if this had been done. Since positive findings occurred in 72.6 per cent of the cases it should be a routine procedure to take films in all suspected cases.

The conservative nonsurgical management has received sporadic support in recent years. This might lead to serious consequences if the cases are not well selected. It is not unusual at operation to find a loosely adherent plug at the site of perforation or a thinly walled off area in close proximity. The margin of safety is so thin in these cases that one wonders if the supporters of this type of management are not more radical than the advocates of surgery.

Since January, 1945, there have been 81 operative cases which are included in this report with 4 deaths for a 4.9 per cent mortality rate. In the light of such statistics, which undoubtedly represent the experience generally, one raises the question of whether surgery is not the more conservative approach. The mortality rate of necessity will be higher on the staff service since these patients are much poorer risks.

It is fair to deduce that over a given period of time the operative mortality rate will be higher in the group that has additional procedures to simple closure of a perforation. In this group gastric resection was not performed, but the experience with pyloroplasty, gastroenterostomy, and appendectomy justify this contention. One might accept the increased risk if the afore-mentioned procedures affected the natural course of the disease. From our experience it appears that in many instances the patient ended up with an additional disease.

In the cases followed, the aftermath revealed a much higher rate of sequelae than was expected at the beginning of this study. It is certain, however, that this incidence would have been reduced if the patients had been on a strict ulcer regime following closure of the perforation. This is borne out by the fact that those patients who returned with active ulcer responded satisfactorily to such a regime. A number of the patients with pyloric obstruction and hemorrhage have been asymptomatic and it is not unlikely that the incidence of surgery would have been less in these groups had they not waited until complications developed before starting treatment.

The review of the patients who developed sequelae revealed that a fairly high proportion developed these symptoms in a relatively short time after closure. This immediately raises the question of whether gastric resection should be performed at the time of perforation. Although recent reports are enthusiastic for this approach it seems to be associated with an unsurgical principle. The technical danger of turning in an acutely inflamed duodenum should not be accepted without reservation. It would seem more reasonable to advise gastric resection after the pathologic process has resolved itself.

SUMMARY

1. A total of 249 cases of acute perforation of a duodenal ulcer occurring at the Genesee and Strong Memorial Hospitals are reviewed.

2. Major sequelae developed in 65.1 per cent of 167 cases followed.

3. In 27.5 per cent of the 109 cases with major sequelae the symptoms recurred within six months of closure.

4. Definitive surgery became necessary in 36.5 per cent of the 167 cases followed.

5. Additional procedures to simple closure of the perforation exclusive of gastric resection did not reduce the incidence of major sequelae.

6. If more than simple closure is to be considered gastric resection is the only procedure fundamentally sound.

7. Gastric resection should be considered early if the patient remains symptomatic under treatment.

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DISCUSSION

DR. KEITH S. GRIMSON (Durham, N. C.).—Dr. Stabins has given us an excellent review of late results in patients who have had acute perforation of duodenal ulcer. These studies have justified his conclusion that certain patients will require definitive surgery later, and that many do not need subsequent surgery following simple closure of a perforation particularly where there is no obstruction of the duodenum.

The purpose of this discussion is not to debate these observations. Rather it is to present information which bears upon the type of subsequent operation, resection, or vagotomy with gastroenterostomy. Results of general use of either procedure were obtained by questionnaire and reported by the Committee on Surgical Procedures of the American Gastroenterological Association two months ago. The conclusion was that results of resection for duodenal ulcer were definitely superior to those of vagotomy with gastroenterostomy. Those of us who prefer vagotomy with gastroenterostomy studied the lengthy text and the numerous tables in detail.

There were two crucial comparative tables which did not correspond with the original data. The errors on one table decreased the percentage favorable to vagotomy and in the other made percentages for resection more favorable. A critique in press, *Gastroenterology*, was submitted. This indicated that of eight important criteria bearing on results of surgery and most reflecting welfare of patients, five favored vagotomy and gastroenterostomy, one favored resection of more than 70 per cent of the stomach, and two were essentially equal after either operation. The erroneous percentages are admitted by the Committee and they are changing their conclusions. Therefore, perhaps, their important report should not yet be accepted as good evidence that gastric resection is the procedure of choice for those patients requiring operation some time after simple closure. However, perforation of a gastric ulcer or of a duodenal ulcer with obstruction may indicate emergency definitive surgery and in this circumstance subtotal gastrectomy might be the procedure of choice.

DR. MARCUS M. RAVITCH (Baltimore, Md.).—If I may be pardoned for returning to Dr. Stabins' paper, most of you are probably well aware that in the 30's Yudin, of

Moscow, reported almost 300 patients with acute perforations treated primarily by subtotal gastrectomy with a mortality of about 5 per cent, with an uncertain follow-up.

Since then, there has been considerable interest in Europe and some in this country in immediate resection as a primary treatment for perforated ulcer. Encouraged by those results, we have adopted the cautious attitude that in patients already presenting, before the perforation, indications for resection, immediate resection should be performed at the time of perforation, if the patient presents himself sufficiently early; and, added to that group, the patients who come in with a second perforation who also have almost all come in early. In a very small group of patients operated upon almost entirely by the house staff in Baltimore, the results seem to be no different than those from elective subtotal gastrectomy.

I think the great importance of Dr. Stabins' paper is in pointing out the relatively gloomy prognosis for people with perforation and the importance of considering immediate action in the light of our present knowledge of the ulcer problem.

DR. RALPH F. BOWERS (Memphis, Tenn.).—Mr. Chairman, I wish to make two comments about Dr. Stabins' excellent report. We see a great number of cases of perforated ulcer at Kennedy Hospital. We have seen almost as many cases in five years as Dr. Stabins has reported for a longer period of time.

It is obvious to me that you cannot compare mortality figures. Our mortality rate by simple closure ranges in the low level of 2 per cent; but this is not meaningful. All of you are aware of the fact that if you receive patients who have perforated a long period of time before operation and, perhaps more important, who spill large amounts of duodenal contents and food (particularly after a hearty meal), or who have developed fulminating bacterial peritonitis, then the mortality rate in anybody's hands will be exceedingly elevated.

In our experience about 50 per cent of the perforated ulcer patients get into difficulty later. We have not followed these patients long enough yet to know accurately the number who will require gastric resection later, but we recognize that the 50 per cent figure will probably approximate the 65 per cent reported by Dr. Stabins as time passes. Thirty-five per cent should not require further surgery.

I cannot share the enthusiasm of some for performing gastric resection for perforated ulcer at the time of perforation. The perforation is an abdominal catastrophe which substantially has been shown to be handled safely by everybody with simple closure. There are many parts of the country, rural and otherwise, where reports of resection at time of perforation will adversely affect mortality rate.

I will concede that Dr. Stabins, Dr. Ravitch, and many of you here, perhaps all of you, could select your cases well and give a good impression. I feel that this is a dangerous trend. As far as I am concerned, I would recommend teaching our residents, and anyone else who will listen, to do simple closure and save the individual's life, so that definitive surgery can be more safely performed later, if any is needed.

EXTRAVAGAL INFLUENCES ON GASTRIC HYDROCHLORIC ACID SECRETION INDUCED BY STRESS STIMULI

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RECENT clinical[1-3] and experimental[4, 5] observations have indicated that influences of the central nervous system can be exerted upon the secretory functions of the stomach through pathways outside the vagus nerve. As much of the therapeutic armamentarium against pathologic states of the upper gastrointestinal tract in which hypersecretion is a factor is directed against vagally mediated influences (vagotomy, parasympathetic blocking agents), investigations concerning the nature and importance of extravagal mechanisms unaffected by such therapeutic measures attain considerable importance.

There can be little doubt that the formation of peptic ulcers can be precipitated by stress.[6] While vagally mediated stimuli are generally considered to function physiologically in the normal process of digestion, it is probable that they may become pathologic under certain stressful conditions.[7] Abnormalities of pituitary-adrenal function, however, are more commonly associated with the stressed state. Moreover, evidence has been adduced which indicates that extravagal influences affecting hydrochloric acid (HCl) secretion by the stomach emanate from the posterior hypothalamus and course through the pituitary-adrenal system.[5]

The following observations were obtained from experiments designed to study the effect of artificially induced stress on HCl secretion of the stomachs of monkeys. Such a state was induced variously by the administration of ACTH, cortisone, epinephrine, and insulin to the animals. Furthermore, as the insulin test[8] is commonly employed to study HCl secretion clinically, observations on animals exposed to this substance served to offer a comparison between responses of animal and of man, as well as to add information to clarify the mechanism of the procedure itself.

EXPERIMENTAL PROCEDURES

Experiments were made on Macaca mulatta monkeys, 31 animals in all being employed. Each procedure was successfully carried out in from 2 to 6 monkeys to control the observation.

Because of the animal's habit of retaining food in its stomach for long periods of time, it was necessary to feed only glucose and water for twenty-four to forty-eight hours before operative or analytic procedures were undertaken.

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Similar dietary restrictions were necessary for many days after vagotomy as extreme atony of the stomach resulted from such denervation.

Animals were anesthetized with intraperitoneal chloralosane (100 mg. per kilogram of body weight) as this agent was found to be the only one (except cyclopropane) which neither stressed the monkey excessively nor blocked its response to subsequently administered stressing agents.[9] Bilateral vagotomy and/or adrenalectomy, when performed, were done so transabdominally. After adrenalectomy, normal saline (30 c.c.) was administered subcutaneously and cortisone (1 c.c. per kilogram of body weight) was given daily. Animals whose cervical cords were sectioned to block centrally mediated sympathetic impulses required careful and complete nursing care postoperatively. Analytic procedures followed operation when performed by at least forty-eight hours.

Analyses of gastric hydrogen-ion concentration (pH) were made, by means of a Beckman Model G pH Meter, on aspirated samples obtained through a Levin tube, before and every one-half hour after administration of the test substance, for five to seven hours. If the pH of the pretest samples was consistently below 5 because of undue stressing of the animal during preparation, or because of retained food in the stomach, the experiment was abandoned, as the pH of stomach contents in the normal fasting monkey was found to range between 5 and 7.

In many experiments, blood sugar determinations were made on .1 c.c. of blood taken from the tail of the animal at the time each sample of gastric contents was analyzed. For these determinations a modified Anthrone method[10] was employed. Determinations below 45 mg. per cent were required when analysis of stomach contents during the hypoglycemic state was under investigation, and the intravenous injection of 2.7 to 6 units of insulin per kilogram of body weight was necessary to bring about this condition. In certain experiments, the prevention of hypoglycemia after the administration of insulin was accomplished by periodic injection of 50 per cent glucose (3 to 4 Gm. per unit of insulin) into an infusion tube delivering normal saline very slowly into the saphenous vein.

The pH of gastric contents was analyzed under the following experimental conditions:

1. *ACTH and Cortisone Administration.*—ACTH (5 mg. per kilogram of body weight) was injected subcutaneously into normal and into vagotomized animals. Cortisone (5 mg. per kilogram of body weight) was injected intramuscularly into normal and into adrenalectomized animals.

2. *Insulin Hypoglycemia.*—Hypoglycemia was induced in normal animals and in animals who had previously undergone vagotomy, adrenalectomy, or a combination of the two procedures.

3. *Administration of Insulin—Hypoglycemia Prevented.*—An amount of insulin equivalent to that employed in Group 2 was injected into normal and into vagotomized animals. Hypoglycemia was prevented, however, by the administration of glucose.

4. *Administration of Insulin After Autonomic Blocking Procedures.*—SKF 501 (N [9-Fluorenyl]-N-ethyl-B-chlorethylamine hydrochloride) was injected intravenously into normal and into vagotomized animals (8 mg. per kilogram of body weight) twenty-four hours before the experiment. Hypoglycemia was then induced experimentally as in Group 2. Additional analyses were made under hypoglycemic conditions in animals which had previously had vagotomy together with section of the cervical spinal cord.

5. *Epinephrine Injection.*—Epinephrine (.2 mg. per kilogram of body weight) was injected intraperitoneally into normal animals and into animals which had previously had adrenalectomy together with vagotomy.

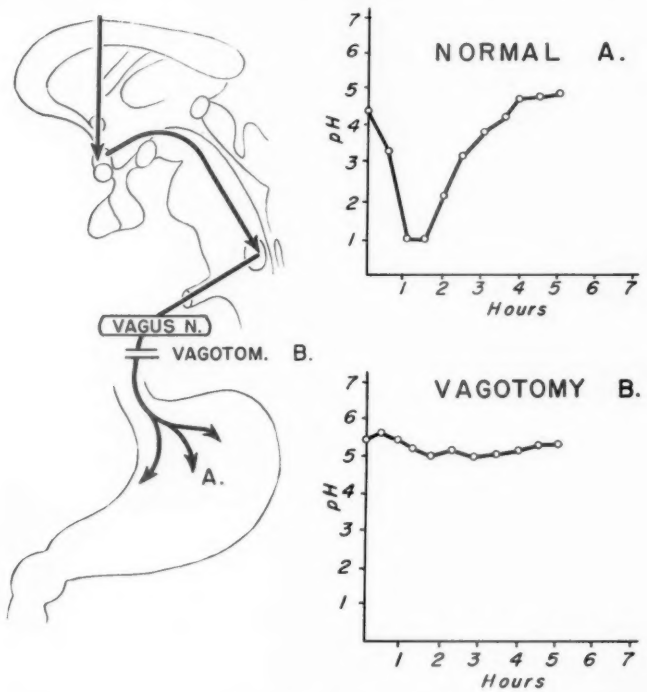

Fig. 1.—The diagram on the left indicates the pathway through which stimulation of the anterior hypothalamus (straight arrow) causes the stomach to secrete hydrochloric acid. Graph A on the right indicates the curve of pH values on such stimulation in the normal animal and Graph B in the vagotomized animal. Note early fall and prompt return to normal.

RESULTS

Previous experiments demonstrated that alteration of the pH of gastric contents followed two distinct patterns upon direct stimulation of the hypothalamus. Stimulation of the anterior hypothalamus resulted in a rapid fall of pH within one-half hour, with a return to normal levels in three hours, the effect being eliminated by section of the vagus nerves (Fig. 1). A second type of response, which was not mediated by the vagus nerve, occurred on stimulation of the posterior hypothalamus. Here the decline in pH resulted only after two to three hours and the return to normal fasting levels was proportionately delayed (Fig. 2). This second type of response was eliminated by adrenalectomy. When both vagi were sectioned and both adrenals removed, all gastric

secretory responses (HCl) to hypothalamic stimulation were eliminated. Hence, it was assumed that all cephalic influences on this phase of the digestive processes were mediated through these two channels.

The results of the experiments described here, in which the responses were induced by stress rather than by direct hypothalamic stimulation, coincide closely with those previously reported. The same two types of response could be induced in the stomach secretions, each being eliminated by appropriate block of its mediating pathway. For the sake of brevity, therefore, the early response will hereafter be described as the early or vagal effect and the delayed response as the late or pituitary-adrenal effect.

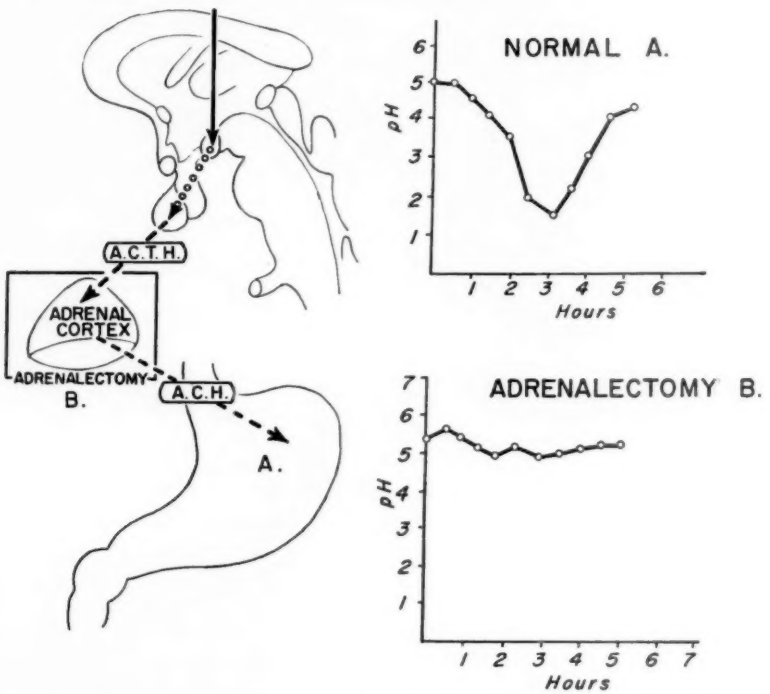

Fig. 2.—The diagram on the left indicates the pathway (circles and dotted lines) through which stimulation of the posterior hypothalamus (solid arrow) causes the stomach to secrete hydrochloric acid. Graph A, on the right, indicates the curve of pH values on such stimulation in the normal animal and Graph B in the adrenalectomized animal. Note delayed fall of curve.

1. The results of the administration of ACTH and of cortisone to the animals are summarized in Fig. 3. Both substances produced a typical pituitary-adrenal effect in the normal animal. ACTH injected into adrenalectomized monkeys produced no gastric response, indicating that the adrenal cortex was essential to the mediation of its influence. The response to cortisone was not altered by vagotomy.

2. The results of the administration of insulin to the animals are illustrated in Fig. 4. The pH graphs of normal animals in which a satisfactory hypoglycemia was induced had features suggesting the superimposition of both early and late responses (Fig. 4, *A*). That both effects were indeed activated was indicated by graphs of responses in the operated animals. Under identical

test conditions, vagotomized animals showed only a pituitary-adrenal response (Fig. 4, *B*) while adrenalectomized animals displayed a pure vagal response (Fig. 4, *C*). Moreover, no response whatever was obtained in animals which had previously been subjected to both vagotomy and adrenalectomy (Fig. 4, *D*).

3. The experiment performed on animals in Group 3 (insulin and glucose) was devised to determine, if possible, whether the induced hypoglycemia or the insulin itself was responsible for the secretion of HCl by the stomach as described in Group 2. Of eight preparations examined, neither normal (Fig. 5, *A*), nor vagotomized (Fig. 5, *B*), animals showed a response to insulin when hypoglycemia was prevented, even though large amounts (10 units) were administered. It can only be concluded that in these experiments, hypoglycemia

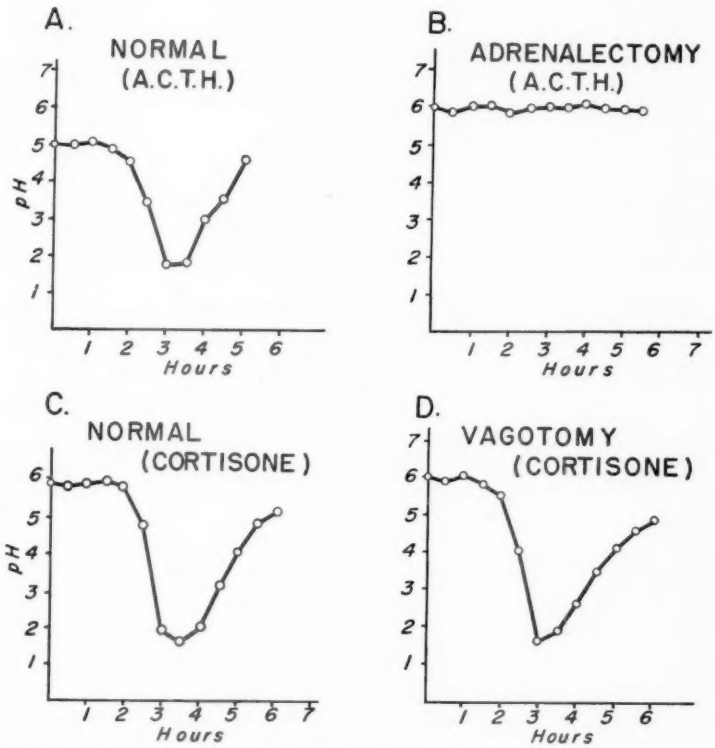

Fig. 3.—The pH values of gastric contents are indicated after the administration of ACTH to normal (*A*) and adrenalectomized (*B*) monkeys and of cortisone to normal (*C*) and vagotomized (*D*) animals. Note delayed fall of pH which is blocked by adrenalectomy (*B*).

activated both early and late responses, though indirect evidence has been adduced which indicates that the pituitary-adrenal effect should be sensitive to insulin in the absence of hypoglycemia.[9]

4. Little information has existed concerning the function of the adrenal medulla in the mechanism of HCl elaboration. These experiments were conducted to explore the role of the sympathetico-adrenal (medulla) system in the gastric secretory response to hypoglycemic stress. Previous evidence has indicated that secretion of HCl on stimulation of the hypothalamus is mediated only by the pituitary-adrenal (cortical) or by the vagal pathways, excitatory

influences not being conducted, apparently, over the sympathetic nerves. Thus a late effect was obtained in vagotomized animals, whether or not their cephalic sympathetic outflow was obstructed by transection of the cervical spinal cord.[5] When insulin hypoglycemia was induced in similar preparations (vagotomy plus cervical cord transection), the delayed secretion of HCl occurred without distortion (Fig. 6, *C*). Cephalic outflow over the sympathetic nervous system, therefore, would not appear to participate in this response as elicited either by central stimulation or induced stress.

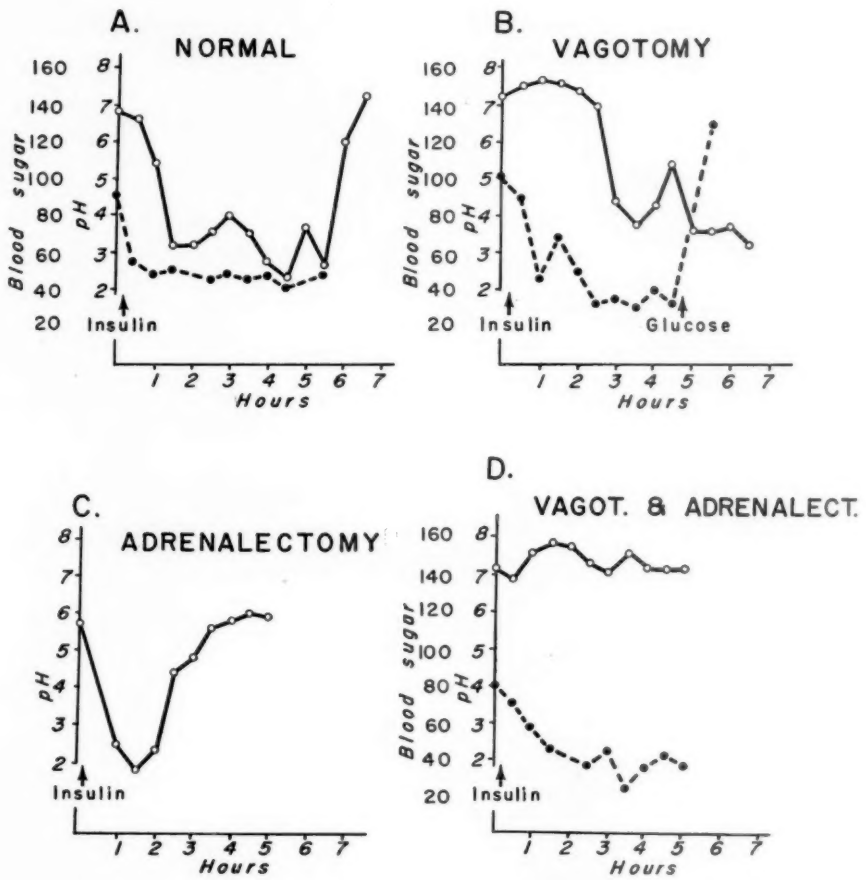

Fig. 4.—Diagrams show the effect of insulin on gastric hydrochloride acid secretion. The pH values (solid lines) and blood sugar determinations (dotted lines) are indicated on administration of insulin to normal (*A*) and to operated (*B, C, D*) animals. Note the early fall and delayed return to normal of pH in the normal animal. Vagotomy obliterates the early and adrenalectomy the late effects of insulin.

Adrenergic humoral mechanisms, conversely, appeared to be implicated in the late response induced by hypoglycemic stress. The unvagotomized animals previously injected with SKF 501, a potent adrenergic blocking agent,[11] exhibited a normal early response when stressed (Fig. 6, *A*), the late effect having been eliminated. Similarly, vagotomized animals protected with the same substance showed no fall in gastric pH on induced hypoglycemia, both early and

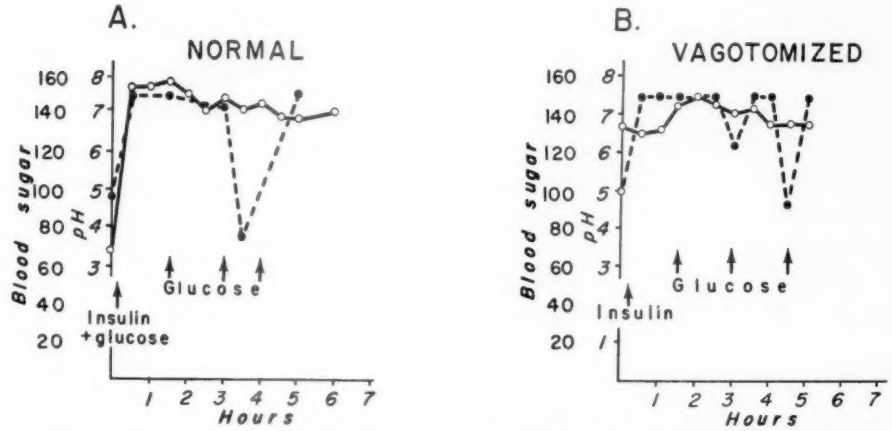

Fig. 5.—The secretion of hydrochloric acid (solid line) is prevented in normal (*A*) and vagotomized (*B*) animals on administration of insulin when glucose is added to prevent hypoglycemia (dotted lines).

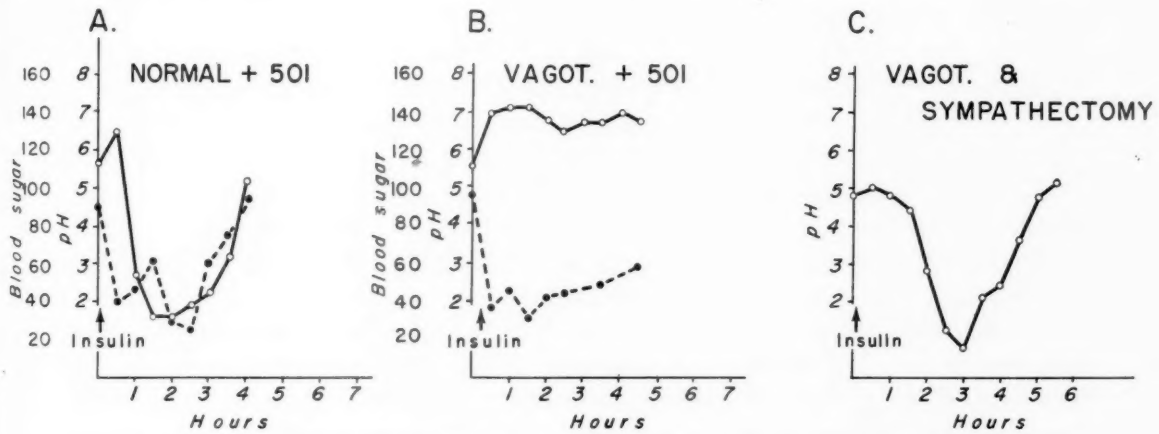

Fig. 6.—Diagrams show effect of autonomic blocking on insulin-induced HCl secretion. Adrenergic blocking agent SKF 501 administered to animal prevents the pituitary-adrenal (*B*) response of hydrochloric acid secretion to insulin hypoglycemia but not the vagal (*A*) response. Blockade of cephalic sympathetic outflow by cervical spinal cord section does not effect the late response (*C*).

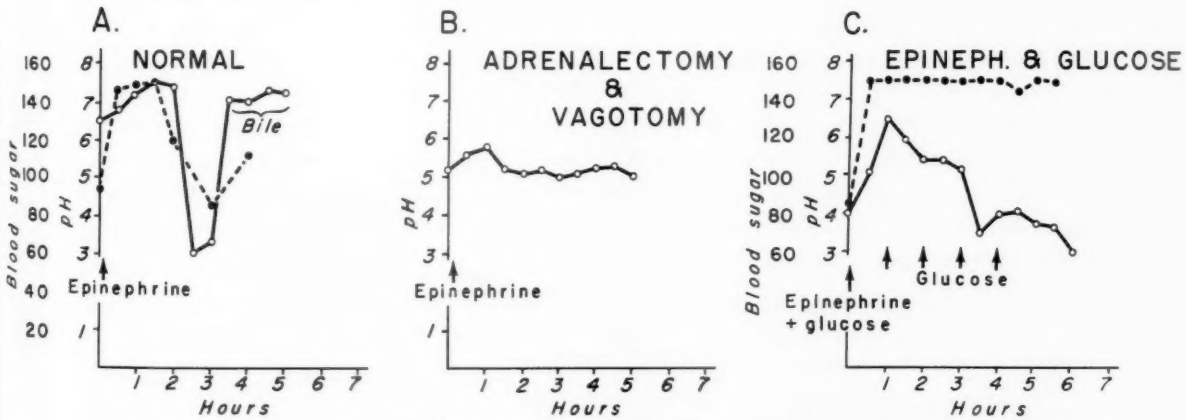

Fig. 7.—Injection of epinephrine causes a delayed response of hydrochloric acid secretion by the stomach (*A*) which requires the presence of the adrenal cortex for the action to take place (*B*). The response to epinephrine does not require an associated hypoglycemia (*A*), nor is it altered by the administration of glucose to the animal.

late responses having been blocked. These observations suggest, therefore, that epinephrine elaborated by direct or reflex stimulation of the adrenal medulla initiates the pituitary-adrenal (cortical) response to hypoglycemia.

5. Evidence from Group 4 to the effect that the adrenal medulla was, at least alternatively, implicated in the late response, suggested that the effect of epinephrine on HCl secretion be studied. Injection of this substance was found to induce a pituitary-adrenallike response (Fig. 7, *A*) which was eliminated by adrenalectomy (Fig. 7, *B*). It seems clear, therefore, that the response was not due to the direct action of epinephrine on the stomach, but that it required the presence and participation of the adrenal cortex.

DISCUSSION

It is probable that many disturbances of function participate in the etiology of peptic ulcer. Among such abnormalities perhaps implicated are vascular changes, injuries, disturbance in the production of mucus, pepsin, or intrinsic hormones, alterations in motility, etc. Recent extensive reviews on the subject, however, are in general agreement concerning the importance of secretion of HCl by the stomach in the pathologic processes underlying the condition.[12, 13] It is becoming increasingly apparent that the nervous system is implicated directly (psychologic stress) or indirectly (physical stress) in many, if not all, of the abnormalities of function leading to ulceration. The present investigation was undertaken in animals, therefore, to explore the role of neural or neuroendocrine mechanisms responsible for the secretion of HCl under conditions which might be considered to simulate stress situations in man.

Classically, there have been described three stages in secretion of HCl by the stomach during normal alimentation. Of these, the cephalic phase, presumably representing the participation of the central nervous system in the digestive process, is said to act wholly,[7] or in large part,[14] by way of the vagus nerve, and to account for approximately 45 per cent of the total acid secreted. It is possible or even probable that during normal alimentation parasympathetic stimuli may exclusively initiate acid secretion, yet there is overwhelming evidence that such vagal discharges do not represent the only means by which brain mechanisms can cause the stomach to pour out HCl. Thus, it has been clearly demonstrated that in animals,[5] and probably in man,[1] marked increase in HCl secretion can be mediated by the posterior hypothalamic-pituitary-adrenal system even though the stomach is completely vagotomized. It is not possible to state as yet whether or not this humoral system functions in this secretory capacity under normal physiologic situations, but there is considerable evidence to indicate that it is primarily discharged under conditions in which the individual is subjected to unusual or stressful situations. As pathologic conditions of the upper gastrointestinal tract are frequently associated temporally with such stressful situations, additional information becomes important concerning secretory propensities of the pituitary-adrenal system.

It has been shown[9] that direct stimulation of that part of the posterior hypothalamus which causes the stomach to secrete HCl produces, in addition, an

eosinopenia and other manifestations of the stressed state. Moreover, during experimentally induced stress (anoxia, hypoglycemia, injection of epinephrine) a tremendous augmentation of spontaneous electrical discharge can be recorded from this same portion of the hypothalamus. As this augmented electrical discharge was confined to a very small area of the posterior hypothalamus, it seemed reasonable to suppose that the stressing agents administered produced their systemic effect by action on this area particularly as its direct stimulation produces the same physical changes. These effects have been shown to be produced through the elaboration of ACTH by the anterior pituitary and, subsequently, ACH by the adrenal cortex, which effector substances work only toward target organs.

It may be presumed, therefore, that the administration of insulin to an animal evoked a delayed secretion of HCl by the stomach through activation of the posterior hypothalamus. This effect, as did the early or vagal response, appeared to be the result of the hypoglycemia induced rather than of any direct stimulus of the insulin itself. In both instances, no response occurred if the insulin was covered with glucose.

While the cerebral sympathetic outflow doubtless participates in motility, vasomotor activity, etc., of the gastrointestinal tract,[15] the evidence from these experiments indicated that sympathetic blockade (cervical cord section) interfered in no way with secretion of HCl by the stomach under the conditions tested. It appeared, however, that, in all probability, the adrenal medulla was implicated in the late secretory response of the stomach to insulin hypoglycemia. Thus, an agent which blocked the effect of epinephrine secreted by the adrenal gland also blocked the late response of gastric secretion to hypoglycemia. Such being the case, the possibility existed that the elaboration of epinephrine was required for activation of the effect produced on secretion by the hypoglycemic state. It was easily demonstrated that the delayed effect could be produced by the administration of epinephrine itself to the animals, but evidence has been presented from experiments in rats[16] that pituitary-adrenal discharges can be evoked by insulin in demedullated animals. However, attempts to repeat these observations in the monkey so far suggest that in this animal the elaboration of epinephrine is necessary for the late secretory effect. If such is the case, the mechanism for this late effect must be diagrammed as in Fig. 8.

There is evidence to indicate that pituitary-adrenal mechanisms similar to these described in animals exist in man. The observations of Gray[1, 2] and of Halstead[3] document the adverse effect upon peptic ulcer formation of the administration of ACTH and ACH to certain patients. Moreover, analyses of the gastric response of patients to the administration of insulin and of epinephrine were found[17] to follow quite closely responses in the above-described animals. Whether or not such extravagal cephalic influences are important in clinical gastrointestinal pathology must await further observation.

It appears, should clinical extrapolation of these experimental data become feasible, that the problem of peptic ulcer may become complicated rather than simplified. It is easy to see how physical and emotional stress could effect gastric

physiology in a variety of ways (Fig. 9). Delayed secretion of HCl by the stomach, as mediated by the pituitary-adrenal system, may be considered a manifestation of stress. As such, the expressions of its influence on the gastrointestinal tract would be abnormal, as distinct from those conducted by way of the vagus nerve which presumably are exerted daily in the normal processes of alimentation. The degree to which these basically normal vagal influences can become pathologic under conditions of stress must be further evaluated.

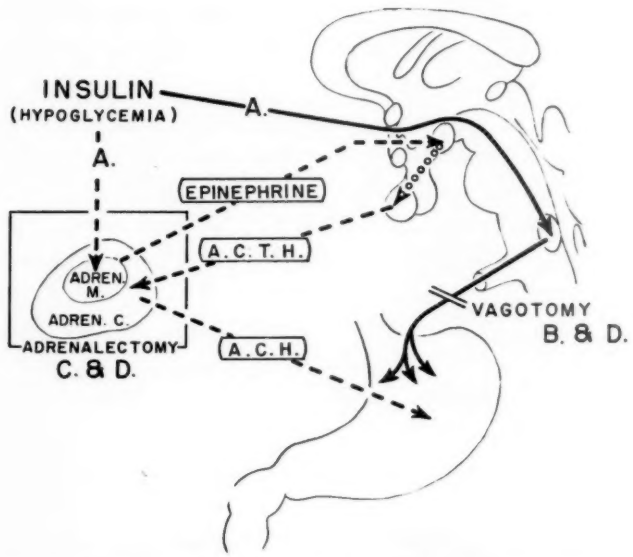

Fig. 8.—The vagal (solid lines) and pituitary-adrenal (dotted lines) mechanisms whereby insulin hypoglycemia causes stomach to secrete hydrochloric acid are diagrammed. The letters *A, B, C* and *D* refer to the graphs in Fig. 4 and humoral substances (blocked) in Figs. 2 and 7 in which responses under designated conditions are documented.

While it has heretofore been considered that the cephalic phase of HCl secretion is subserved by a single (vagal) neural mechanism, the present results show plainly that an additional efferent channel exists by which the brain can excite gastric hypersecretion. Both vagal and humoral influences emanate from hypothalamic areas readily available to the rigors of emotional turmoil by virtue of their known rich connections with other cerebral structures.[18, 19]

It is noteworthy that present-day attacks against the resulting gastric hypersecretion sacrifice the outflow employed in normal digestion rather than the alternate one which much physiologic data indicate is that active in response to stress. There has, however, been no information adduced as yet which indicates that late mischief persists following vagal denervation. Moreover, as only 13 per cent of the postvagotomy patients reported by Rowe and associates[20] displayed abnormally high HCl readings after the injection of insulin, it may be that the stronger influence to gastric secretion is conveyed by way of the vagus nerve. Nevertheless, it seems logical to evaluate therapeutically the effect of adrenergic blocking agents in the peptic ulcer problem at least in patients where vagal blockade is ineffective. Such investigation is now being undertaken.

At present, no other peripheral attacks, than those against vagally mediated influences, appear to eliminate more effectively some portion of the cephalic influences causing hypersecretion. Such attacks should be made, however, with the knowledge that even after vagal denervation of the stomach important secretory influences may persist, perhaps to the degree that symptomatology may occasionally not be eliminated.

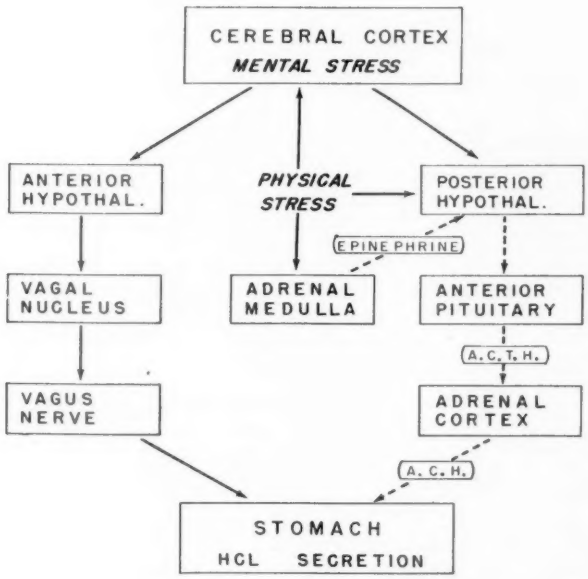

Fig. 9.—The effects of physical and mental stresses on the secretion of hydrochloric acid by the stomach are diagrammed on the basis of evidence adduced in these experiments.

SUMMARY

1. Experiments in monkeys indicate that the stomach can be induced to secrete hydrochloric acid on stimulation of the hypothalamus through two distinct routes. Excitation of the anterior hypothalamus produces an early fall of pH, the stimulus being conducted by way of the vagus nerve. Activation of the posterior hypothalamus exerts its effects through the pituitary-adrenal system, causing a delayed secretion of hydrochloric acid.

2. Agents known to induce a condition of stress in animals have been shown to cause the secretion of hydrochloric acid by the stomach. Insulin hypoglycemia exerts its effect by exciting both vagal and pituitary-adrenal mechanisms. The secretion of epinephrine by the adrenal medulla, its stimulation of the posterior hypothalamus, and the subsequent elaboration of ACTH and ACH appear to be the successive events responsible for the extravagal secretion of hydrochloric acid evoked by hypoglycemia.

3. The possible extrapolation of these simulated conditions of physical and mental stress to clinical problems was discussed.

We wish to express our appreciation to Dr. C. W. Sawyer for his valuable suggestions, to Martha Rock for assisting with the laboratory determinations, and to Charles Bridgeman, Thomas Masterson, and Tim Dodge for preparing the figures.

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Review of Recent Meetings

MEETING OF THE SOCIETY OF UNIVERSITY SURGEONS

FEB. 12-14, 1953, ST. LOUIS, MO.

K. S. GRIMSON, M.D., DURHAM, N. C.

THE fifteenth meeting of the Society of University Surgeons was held in St. Louis, Mo. on Feb. 12, 13, and 14, 1953. The Society was the guest of Washington University School of Medicine. Dr. Franklin E. Walton extended the regrets of Dr. Carl E. Moyer who was in South America and unable to officiate. Welcoming remarks were extended by Dr. Robert A. Moore, dean. The program for Thursday, Feb. 12, was arranged by Washington University School of Medicine in conjunction with St. Louis University School of Medicine. Dr. Evarts A. Graham and Dr. Franklin E. Walton presided over the morning program. Subjects and authors were as follows:

1. Experimental Studies on the Blood Spinal Fluid Barrier—Dr. H. G. Schwartz, Dr. W. B. Seaman, and Dr. F. Kerr
2. Studies of the Re-expanded Lung After Prolonged Atelectasis—Dr. T. H. Burford and Dr. W. R. Webb
3. Functional Studies of the Lung After Prolonged Venous Congestion—Dr. J. G. Mudd and Dr. D. R. Burke, Jr. (St. Louis University)
4. Observations on Experimental Pulmonary Embolism—Dr. J. R. Smith
5. Transplantation of Homologous Endocrine Tissue to the Anterior Chamber of the Eye—Dr. J. T. Dameron (St. Louis University)
6. Urinary Steroids in Adrenal Hyperplasia and Adrenal Tumors—Dr. W. M. Allen
7. Experimental Study of the Effect of Fluorides on the Healing of Fractures —Dr. R. T. Odell and Dr. J. A. Key
8. Resumption of Heart Beat in Chick Embryos Frozen in Liquid Nitrogen—Friar Basile Luyet (St. Louis University)
9. The Metabolism of Radioactive Male and Female Sex Hormones—Dr. E. A. Doisy, Jr., and Dr. W. M. Elliott (St. Louis University)
10. Enzymatic Hydrolysis of Conjugates of Urinary Steroids—Dr. R. A. Kinsella, Jr., Dr. P. A. Katzman, and Dr. E. A. Doisy (St. Louis University)
11. Experimental Production of Carcinoma With Cigarette Tars—Dr. Evarts A. Graham
12. Observations on the Site of Obstruction of Portal Hypertension—Dr. L. V. Mulligan (St. Louis University)
13. Management of Bone Involvement in Intraoral Cancer—Dr. L. T. Byars
14. Total and Fractional Blood Levels of Adrenal Steroids Following Surgery—Dr. J. Moncrief, Dr. T. E. Weichselbaum, and Dr. Robert Elman
15. The Effect of ACTH on Plasma Electrolytes—Dr. M. J. Pareira

After adjournment for lunch the afternoon program was presented. Dr. Duff Allen and Dr. John Modlin presided. Subjects and authors were as follows:

1. The Cellular Immunology of Bacteremia—Dr. W. B. Wood
2. Newer Concepts of the Pathogenesis of Idiopathic Thrombocytopenic Purpura—Dr. W. J. Harrington

3. Splenectomy in Patients With Primary Bone Marrow Failure and With Secondary Hemolytic Anemia, Granulocytopenia, or Thrombocytopenia: Selection and Pathologic Physiology—Dr. V. Loeb, Jr.
4. Experimental Observations on the Drug Urokon—Dr. C. B. Mueller and Dr. A. Porporis
5. Ureteral Electrokymography—Dr. H. Butcher and Dr. William Sleator
6. Microchemical Techniques in the Study of Brain Tumors—Dr. Oliver Lowry
7. An Experimental and Clinical Study on Intravenous Coconut Water Administration—Dr. Ben Eiseman
8. Sweating Patterns and Vasomotor Responses Induced by Stimulation of the Sympathetic Trunk in Man; Clinical Applications—Dr. K. B. Coldwater, Dr. J. W. Cox, Dr. W. C. Randal, Dr. W. F. Alexander, and Dr. A. B. Hertzman (St. Louis University)
9. The Role of Temperature in the Control of Surface Bleeding—Dr. V. Willman (St. Louis University)
10. Substitution of the Superficial Femoral Artery for Ipsilateral Common and External Iliac Artery—Dr. C. E. Lischer and Dr. A. McAfee
11. Variations in Total Body Water During Surgery and Following the Administration of Hexamethonium for Induced Hypotension—Dr. Charles Eckert, Dr. T. E. Weichselbaum, and Dr. L. Molano

Papers by members of the Society were presented on the last two days of the meeting. All but one are published in this number of SURGERY. The article by Dr. Dobyns and Dr. Steelman, which the authors decided was more appropriate for *Endocrinology*, has been abstracted here.

The Thyroid-stimulating Hormone (TSH) of the Anterior Pituitary as Distinct From the Exophthalmos-producing Substance (EPS), Brown M. Dobyns, M.D.,* Cleveland, Ohio, and Sanford L. Steelman, M.D., Chicago, Ill.**—Certain former observations led to the suspicion that experimental exophthalmos and thyroid hyperplasia were produced by different substances rather than a single one in pituitary extract. A method of assaying the exophthalmos-producing quality of pituitary preparations in fish has been modified from that of Albert. A large number of pituitary fractions obtained during the course of preparation or purification of other pituitary hormones were procured.† By screening these preparations for exophthalmos-producing activity, it was found that the amount of such activity was not always parallel to the amount of thyroid-stimulating hormone (TSH). Information gleaned from the various chemical procedures previously used in the preparation of these fractions led to the specific separation of TSH from the exophthalmos-producing substance (EPS) by trichloroacetic acid precipitation. TSH was obtained free of EPS and EPS was obtained relatively free of TSH. The data indicated that there are two independent pituitary factors which were previously regarded as thyrotropic hormone: one produces exophthalmos; the other produces thyroid hyperplasia.

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**Fundamental Research Department, The Armour Laboratories, Chicago.

†Fractions obtained from The Armour Laboratories.

Contents—(Continued from front cover)

Experimental Tuberculosis. IV. Effects of Occlusion of Pulmonary Veins on Tuberculosis in Monkeys. H. William Scott, Jr., M.D., Nashville, Tenn., C. Rollins Hanlon, M.D., St. Louis, Mo., and Byron J. Olson, M.D., and C. F. T. Mattern, M.D., Bethesda, Md. ---------- 426

Combined Adrenalectomy-Sympathectomy in the Treatment of Patients With Essential Hypertension. H. A. Zintel, M.D., J. A. Mackie, M.D., W. A. Jeffers, M.D., C. C. Wolferth, M.D., A. G. Hills, M.D., A. M. Sellers, M.D., and J. H. Hafkenschiel, M.D., Philadelphia, Pa. ---------- 438

Observations on Experimental Bile Peritonitis. Robert M. Miles, M.D., and Howard S. Jeck, M.D., Memphis, Tenn. ---------- 445

Fluid Kinetics Following Thermal Burns in Man. James D. Hardy, M.D., William A. Neely, M.D., Frank C. Wilson, Jr., M.D., E. Pervis Milnor, M.D., and Harwell Wilson, M.D., Memphis, Tenn. ---------- 457

Investigations Into the Role of Heparin in Proliferative Tissue Reactions. I. Increased Heparin Tolerance in Patients With Burns and Keloids. David W. Robinson, M.D., and Tom Reid Hamilton, M.D., Kansas City, Kan. With the Technical Assistance of Esther Roth, M.A., Freeman Claxton, M.S., Daniel Azarnoff, M.S., and Grace Paul, M.T. ---------- 470

Relationship of Sonically Disrupted Platelets to Serum Vasoconstrictor Activity. Jack W. Cole, M.D., Harry Livingston, M.D., Charles W. Loughry, M.D., and William D. Holden, M.D., Cleveland, Ohio ---------- 482

Bio-Electric Phenomena as Etiological Agents in Intravascular Thrombosis. Philip N. Sawyer, M.D., Philadelphia, Pa., and Lieutenant (j.g.) James W. Pate, Medical Corps, United States Naval Reserve, Bethesda, Md. ---------- 491

Studies on Lysis of Experimental Pulmonary Emboli Using Trypsin. William W. Shingleton, M.D., William G. Anlyan, M.D., and Karleen C. Neill, M.D., Durham, N. C. ---------- 501

The Effects of Adrenal Medullectomy and Sympathectomy on the Circulatory Dynamics of Normal Dogs. Victor Richards, M.D., Russell Lee, M.D., and Walter Goggans, M.D., San Francisco, Calif. ---------- 510

Metastasis From Mammary Carcinoma to the Supraclavicular and Internal Mammary Lymph Nodes. J. J. McDonald, M.D., C. D. Haagensen, M.D., and A. P. Stout, M.D., New York, N. Y. ---------- 521

Clinical and Metabolic Studies of Bilateral Adrenalectomy for Advanced Cancer in Man. Olof H. Pearson, M.D., Willet F. Whitmore, Jr., M.D., Charles D. West, M.D., Joseph H. Farrow, M.D., and Henry T. Randall, M.D., New York, N. Y. -- 543

Portal Venography Via the Portal and Percutaneous Splenic Routes. Louis M. Rousselot, M.D., Francis F. Ruzicka, M.D., and G. A. Doehner, M.D., New York, N. Y. ---------- 557

Experiences With Portacaval Anastomosis in the Treatment of Portal Hypertension. Charles B. Ripstein, M.D., Brooklyn, N. Y. ---------- 570

The Management of Cirrhosis of the Liver and Ascites With Particular Reference to the Portacaval Shunt Operation. David V. Habif, M.D., Henry T. Randall, M.D., Med.Sc.D.(Surg.), and Harry S. Soroff, M.D., New York, N. Y. ---------- 580

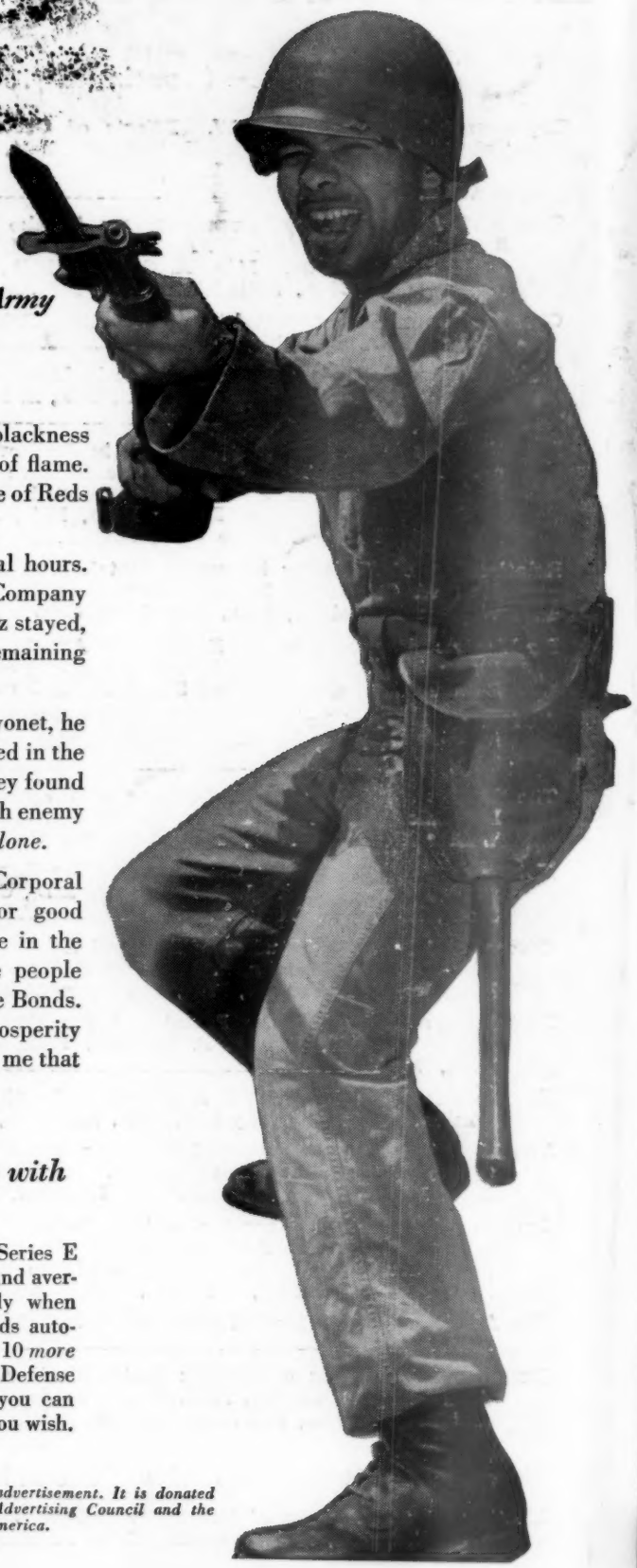
Studies of Combined Vascular and Neurological Injuries. II. The Effect of Arterial Ligation and of Sympathetic Denervation Upon Return of Function After Crushing the Sciatic Nerve of the Rat. Arnold Kunkler, M.D., and Harris B. Shumacker, Jr., M.D., Indianapolis, Ind. ---------- 607

The Aftermath of Perforated Duodenal Ulcer. Samuel J. Stabins, M.D., Rochester, N. Y. ---------- 614

Extravagal Influences on Gastric Hydrochloric Acid Secretion Induced by Stress Stimuli. J. D. French, M.D., R. L. Longmire, A.B., R. W. Porter, M.D., Ph.D., and H. J. Movius, M.D., Long Beach, Calif. ---------- 621

Review of Recent Meetings

Meeting of the Society of University Surgeons, Feb. 12-14, 1953, St. Louis, Mo. K. S. Grimson, M.D., Durham, N. C. ---------- 633



Corporal
Rodolfo P. Hernandez, U.S. Army
Medal of Honor

0200 HOURS! Suddenly the pre-dawn blackness on Hill 420 split into crashing geysers of flame. Yelling, firing, hurling grenades, a horde of Reds pushed up the hill toward G Company.

A hot fire fight began, lasting several hours. Finally, suffering heavy casualties, G Company began to withdraw. Corporal Hernandez stayed, throwing grenades and firing his remaining rounds.

Then his M-1 jammed. Fixing his bayonet, he leaped out of his foxhole and disappeared in the darkness toward the attacking Reds. They found him in the morning, wounded, ringed with enemy dead. But he had stopped the attack—*alone.*

"A man couldn't fight at all," says Corporal Hernandez, "if he weren't fighting for good things—peace, and a job, and a chance in the world. That's why I'm thankful to the people who've put so many billions into Defense Bonds. For I believe Bonds are a stockpile of prosperity for our country. A guarantee to men like me that we can come home to a secure future."

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